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 NEWS  1          Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2          "Ask CAS" for self-help around the clock
 NEWS  3  SEP 09  CA/CAplus records now contain indexing from 1907 to the
                  present
 NEWS  4  DEC 08  INPADOC: Legal Status data reloaded
 NEWS  5  SEP 29  DISSABS now available on STN
 NEWS  6  OCT 10  PCTFULL: Two new display fields added
 NEWS  7  OCT 21  BIOSIS file reloaded and enhanced
 NEWS  8  OCT 28  BIOSIS file segment of TOXCENTER reloaded and enhanced
 NEWS  9  NOV 24  MSDS-CCOHS file reloaded
 NEWS 10  DEC 08  CABA reloaded with left truncation
 NEWS 11  DEC 08  IMS file names changed
 NEWS 12  DEC 09  Experimental property data collected by CAS now available
                  in REGISTRY
 NEWS 13  DEC 09  STN Entry Date available for display in REGISTRY and CA/CAplus
 NEWS 14  DEC 17  DGENE: Two new display fields added
 NEWS 15  DEC 18  BIOTECHNO no longer updated
 NEWS 16  DEC 19  CROPU no longer updated; subscriber discount no longer
                  available
 NEWS 17  DEC 22  Additional INPI reactions and pre-1907 documents added to CAS
                  databases
 NEWS 18  DEC 22  IFIPAT/IFIUDB/IFICDB reloaded with new data and search fields
 NEWS 19  DEC 22  ABI-INFORM now available on STN
 NEWS 20  JAN 27  Source of Registration (SR) information in REGISTRY updated
                  and searchable
 NEWS 21  JAN 27  A new search aid, the Company Name Thesaurus, available in
                  CA/CAplus
 NEWS 22  FEB 05  German (DE) application and patent publication number format
                  changes
 NEWS 23  MAR 03  MEDLINE and LMEDLINE reloaded
 NEWS 24  MAR 03  MEDLINE file segment of TOXCENTER reloaded
 NEWS 25  MAR 03  FRANCEPAT now available on STN
 NEWS 26  MAR 29  Pharmaceutical Substances (PS) now available on STN
 NEWS 27  MAR 29  WPIFV now available on STN
 NEWS 28  MAR 29  No connect hour charges in WPIFV until May 1, 2004
 NEWS 29  MAR 29  New monthly current-awareness alert (SDI) frequency in RAPRA

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               MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 3 MARCH 2004
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FILE 'HOME' ENTERED AT 19:42:02 ON 01 APR 2004

=> file uspatful
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FULL ESTIMATED COST                                        0.21          0.21

FILE 'USPATFULL' ENTERED AT 19:42:32 ON 01 APR 2004
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FILE COVERS 1971 TO PATENT PUBLICATION DATE: 1 Apr 2004 (20040401/PD)
FILE LAST UPDATED: 1 Apr 2004 (20040401/ED)
HIGHEST GRANTED PATENT NUMBER: US6715148
HIGHEST APPLICATION PUBLICATION NUMBER: US2004064864
CA INDEXING IS CURRENT THROUGH 1 Apr 2004 (20040401/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 1 Apr 2004 (20040401/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Feb 2004
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Feb 2004

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=> s e3
L1            7 "FRANCHINI GENOVEFFA"/IN

=> d l1,ti,1-7

L1   ANSWER 1 OF 7  USPATFULL on STN
TI      Immunogenicity using a combination of dna and vaccinia virus vector
        vaccines

L1   ANSWER 2 OF 7  USPATFULL on STN
TI      Immunodeficiency recombinant poxvirus

L1   ANSWER 3 OF 7  USPATFULL on STN
TI      Immunodeficiency recombinant poxvirus
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L1 ANSWER 4 OF 7 USPATFULL on STN
TI Molecular clones of HIV-1 viral strains MN-ST1 and BA-L, and uses thereof

L1 ANSWER 5 OF 7 USPATFULL on STN
TI Molecular clones of HIV-1 viral strains MH-ST1 and BA-L, and uses thereof

L1 ANSWER 6 OF 7 USPATFULL on STN
TI Molecular clones of HIV-1 viral strains MN-ST1 and BA-L and uses thereof

L1 ANSWER 7 OF 7 USPATFULL on STN
TI Characterization of replication competent human immunodeficiency type 2 proviral clone HIV-$2_{SBL/ISY}$

=> d l1,cbib,ab,clm,1-3

L1 ANSWER 1 OF 7 USPATFULL on STN
2004:44247 Immunogenicity using a combination of dna and vaccinia virus vector vaccines.
Franchini, Genoveffa, Washington, DC, UNITED STATES
Hel, Zdenek, Rockville, MD, UNITED STATES
Pavlakis, George, Rockville, MD, UNITED STATES
US 2004033237 A1 20040219
APPLICATION: US 2002-258570 A1 20021025 (10)
WO 2001-US13968 20010430
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention relates to improved methods of inducing an immune response for the prevention or treatment of HIV-1 infection by using a nucleic acid vaccine in conjunction with a recombinant viral vaccine, e.g., a poxvirus vaccine, to potentiate and broaden the immune response. The present invention further provides a particularly effective vaccine regimen comprising a DNA vaccine used in combination with a poxvirus virus, especially NYVAC or ALVAC.
CLM What is claimed is:

1. A method of potentiating a CD8+ response to human immunodeficiency virus-1 (HIV-1) epitopes in a human by adminstering a combination of vaccines, said method comprising: administering a nucleic acid vaccine; administering a recombinant pox virus vaccine encoding one or more of the same antigens encoded by the nucleic acid vaccine; wherein the nucleic acid and the recombinant pox virus vaccines enter the cells of the human and intracellularly produce HIV-specific peptides that are presented on the cell's MHC class I molecules in an amount sufficient to stimulate a CD8+ response, and further, wherein administration of the combination of vaccines potentiates the immune response compared to administration of either the nucleic acid or the recombinant pox virus vaccine by itself.

2. A method of claim 1 wherein the vaccine is an attenuated recombinant pox virus vaccine.

3. A method of claim 2 wherein the attenuated recombinant pox virus vaccine is selected from the group consisting of NYVAC and ALVAC.

4. A method of claim 1, wherein the nucleic acid vaccine is a DNA vaccine.

5. A method of claim 1 wherein the HIV-specific peptides are structural viral peptides

6. A method of claim 1 wherein the HIV-specific peptides are non-structural viral peptides.

7. A method of claim 1 wherein the vaccines further comprise an adjuvant.

8. A method of claim 1 further comprising two administrations of nucleic acid vaccine.

9. A method of claim 8 comprising three administrations of the nucleic acid vaccine.

10. A method of claim 1, wherein the nucleic acid vaccine is administered before the recombinant pox virus vaccine.

11. A method of claim 1, wherein the human is infected with HIV-1.

12. A method of claim 11, wherein the human has a viral load of less than 10,000 copies per milliliter.

13. A method of claim 1, wherien the human is not infected with HIV-1.

L1 ANSWER 2 OF 7 USPATFULL on STN

2003:318245 Immunodeficiency recombinant poxvirus.

Paoletti, Enzo, Delmar, NY, UNITED STATES
Tartaglia, James, Schenectady, NY, UNITED STATES
Cox, William I., East Breenbush, NY, UNITED STATES
Gallo, Robert, Baltimore, MD, UNITED STATES
Franchini, Genoveffa, Washington, DC, UNITED STATES
US 2003223987 A1 20031204
APPLICATION: US 2003-441788 A1 20030520 (10)
DOCUMENT TYPE: Utility; APPLICATION.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Attenuated recombinant viruses containing DNA encoding an immunodeficiency virus and/or CTL antigen, as well as methods and compositions employing the viruses, expression products therefrom, and antibodies generated from the viruses or expression products, are disclosed and claimed. The recombinant viruses can be NYVAC or ALVAC recombinant viruses. The DNA can code for at least one of: HIV1gag(+pro)(IIIB), gp120(MN)(+transmembrane), nef(BRU)CTL, pol(IIIB)CTL, ELDKWA or LDKW epitopes, preferably HIV1gag(+pro)(IIIB), gp120(MN) (+transmembrane), two (2) nef(BRU)CTL and three (3) pol(IIIB)CTL epitopes; or two ELDKWA in gp120 V3 or another region or in gp160. The two (2) nef(BRU)CTL and three (3) pol(IIIB)CTL epitopes are preferably CTL1, CTL2, pol1, pol2 and pol3. The recombinant viruses and gene products therefrom and antibodies generated by the viruses and gene products have several preventive, therapeutic and diagnostic uses. DNA from the recombinant viruses are useful as probes or, for generating PCR primers or for immunization. Also disclosed and claimed are HIV immunogens and modified gp160 and gp120.

CLM What is claimed is:

1. A modified recombinant virus, said modified recombinant virus having virus-encoded genetic functions inactivated therein so that the virus has attenuated virulence, yet retained efficacy; said virus further comprising exogenous DNA in a nonessential region of the virus genome, said exogenous DNA encoding at least one immunodeficiency virus epitope.

2. The virus of claim 1 wherein said virus is a poxvirus.

3. The virus of claim 2 wherein the poxvirus is a vaccinia virus.

4. The virus of claim 3 wherein the genetic functions are inactivated by deleting at least one open reading frame.

5. The virus of claim 4 wherein the deleted genetic functions include a C7L-K1L open reading frame, or, a host range region.

6. The virus of claim 5 wherein at least one additional open reading

frame is deleted; and, the additional open reading frame is selected from the group consisting of: J2R, B13R+B14R, A26L, A56R, and I4L.

7. The virus of claim 5 wherein at least one additional open reading frame is deleted; and, the additional open reading frame is selected from the group consisting of: a thymidine kinase gene, a hemorrhagic region, an A type inclusion body region, a hemagglutinin gene, and a large subunit, ribonucleotide reductase.

8. The virus of claim 6 wherein J2R, B13R+B14R, A26L, A56R, C7L-K1L and I4L are deleted from the virus.

9. The virus of claim 7 wherein a thymidine kinase gene, a hemorrhagic region, an A type inclusion body region, a hemagglutinin gene, a host range region, and a large subunit, ribonucleotide reductase are deleted from the virus.

10. The virus of claim 8 which is a NYVAC recombinant virus.

11. The virus of claim 9 which is a NYVAC recombinant virus.

12. The virus of claim 11 wherein the exogenous DNA codes for at least one of: HIV1gag(+pro)(IIIB), gp120(MN)(+transmembrane), nef(BRU)CTL, pol(IIIB)CTL, and ELDKWA or LDKW epitopes.

13. The virus of claim 12 wherein the exogenous DNA codes for HIV1gag (+pro)(IIIB), gp120(MN)(+transmembrane), two nef(BRU)CTL and three pol(IIIB)CTL epitopes; or, two ELDKWA epitopes.

14. The virus of claim 13 wherein the two nef(BRU)CTL and three pol(IIIB)CTL epitopes are: CTL1, CTL2, pol1, pol2 and pol3.

15. The virus of claim 12 wherein the ELDKWA or LDKW epitopes are expressed as part of a region of gp120 or a region of gp160.

16. The virus of claim 15 wherein the ELDKWA or LDKWA epitopes are expressed as part of gp120 V3.

17. A modified recombinant avipox virus which is modified so that it has attenuated virulence in a host; and, which contains exogenous DNA in a nonessential region of the virus genome, said exogenous DNA encoding at least one immunodeficiency virus epitope.

18. The virus of claim 17 wherein said virus is a canarypox virus.

19. The virus of claim 18 wherein the canarypox virus is a Rentschler vaccine strain which was attenuated through more than 200 serial passages on chick embryo fibroblasts, a master seed therefrom was subjected to four successive plaque purifications under agar, from which a plaque clone was amplified through five additional passages.

20. The virus of claim 18 which is an ALVAC recombinant virus.

21. The virus of claim 18 wherein the exogenous DNA codes for at least one of: HIV1gag(+pro)(IIIB), gp120(MN)(+transmembrane), nef(BRU)CTL, pol(IIIB)CTL, and ELDKWA or LDKW epitopes.

22. The virus of claim 18 wherein the exogenous DNA codes for at least one of: HIV1gag(+pro)(IIIB), gp120(MN)(+transmembrane), two nef(BRU)CTL and three pol(IIIB)CTL epitopes; or two ELKDWA epitopes.

23. The virus of claim 21 wherein the ELDKWA or LDKWA epitopes are expressed as part of a region of gp120 or a region of gp160.

24. The virus of claim 23 wherein the ELDKWA or LDKWA epitopes are expressed as part of gp120 V3.

25. The virus of claim 22 wherein the two nef(BRU)CTL and three pol(IIIB)CTL epitopes are: CTL1, CTL2, pol1, pol2 and pol3.

26. The virus of claim 21 which is vCP205 (ALVAC-MN120TMG), vCP264 (ALVAC-MN120TMGN), vCP300 (ALVAC-MN120TMGNP), or vCP1307.

27. vP1313 or vP1319.

28. A method for treating a patient in need of immunological treatment or of inducing an immunological response in an individual comprising administering to said patient or individual a composition comprising a virus as claimed in any one of claims 1, 12, 14, 21, 26 or 27 in admixture with a suitable carrier.

28. A composition for inducing an immunological response comprising a virus as claimed in any one of claims 1, 12, 14, 21, 26 or 27 in admixture with a suitable carrier.

29. A method for expressing a gene product in a cell cultured in vitro comprising introducing into the cell a virus as claimed in any one of claims 1, 12, 14, 21, 26 or 27.

29. An immunodeficiency virus antigen prepared from in vitro expression of a virus as claimed in any one of claims 1, 12, 14, 19, 22 or 23.

30. An antibody elicited by in vivo expression of an antigen from a virus as claimed in any one of claims 1, 12, 14, 19, 22 or 23 or, by administration of an immunodeficiency virus associated antigen from in vitro expression of the virus.

31. An HIV immunogen selected from the group consisting of: HIV1gag(+pro)(IIIB), gp120(MN)(+transmembrane), nef(BRU)CTL, pol(IIIB)CTL, and ELDKWA or LDKW epitopes.

32. The HIV immunogen of claim 31 wherein the ELDKWA or LDKWA is part of a region of gp120 or a region of gp160.

33. The HIV immunogen of claim 32 wherein the ELDKWA or LDKWA is part of gp120 V3.

34. A gp120 or gp160 modified so as to contain an epitope not naturally occurring in gp120 or gp160.

35. The gp120 or gp160 of claim 34 modified so as to contain a B-cell epitope not naturally occurring in gp120 or gp160.

36. The gp120 or gp160 or claim 34 which is a gp120 modified in the V3 loop so as to contain an epitope not naturally occurring on the gp120 V3 loop.

37. The gp160 or gp120 of claim 36 wherein teh epitope is a B-cell epitope.

38. The gp160 or gp120 or claim 36 wherein the eiptope is ELDKWA or LDKWA.

39. The gp160 or gp120 of claim 34 which is a gp120 modified to contain at least one of HIV1gag(+pro)(IIIB), gp120(MN) (+transmembrane), nef(BRU)CTL, pol(IIIB)CTL, and ELDKWA or LDKW epitopes.

40. The gp160 of gp120 of claim 39 wherein the gp120 is modified in the V3 loop to contain the epitope.

L1 ANSWER 3 OF 7 USPATFULL on STN

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Tartaglia, James, Schenectady, NY, United States
Cox, William I., East Greenbush, NY, United States
Gallo, Robert, Baltimore, MD, United States
Franchini, Genoveffa, Washington, DC, United States
Virogenetics Corporation, Troy, NY, United States (U.S. corporation)
US 6596279 B1 20030722
APPLICATION: US 1998-136159 19980814 (9)
DOCUMENT TYPE: Utility; GRANTED.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Attenuated recombinant viruses containing DNA encoding an immunodeficiency virus and/or CTL antigen, as well as methods and compositions employing the viruses, expression products therefrom, and antibodies generated from the viruses or expression products, are disclosed and claimed. The recombinant viruses can be NYVAC or ALVAC recombinant viruses. The DNA can code for at least one of: HIV1gag(+pro)(IIIB), gp120(MN)(+transmembrane), nef(BRU)CTL, pol(IIIB)CTL, ELDKWA or LDKW epitopes, preferably HIV1gag(+pro)(IIIB), gp120(MN) (+transmembrane), two (2) nef(BRU)CTL and three (3) pol(IIIB)CTL etpitopes; or two ELDKWA in gp120 V3 or another region or in gp160. The two (2) nef(BRU)CTL and three (3) pol(IIIB)CTL epitopes are preferably CTL1, CTL2, pol1, pol2 and pol3. The recombinant viruses and gene products therefrom and antibodies generated by the viruses and gene products have several preventive, therapeutic and diagnostic uses. DNA from the recombinant viruses are useful as probes or, for generating PCR primers or for immunization. Also disclosed and claimed are HIV immunogens and modified gp160 and gp120.

CLM What is claimed is:

1. A recombinant poxvirus comprising exogenous DNA encoding at least one Lentivirus epitope, wherein the poxvirus is a vaccinia virus having J2R, B13R+B14R, A26L, A56R, C7L-K1L and I4L are deleted from the virus; or a thymidine kinase gene, a hemorrhagic region, an A type inclusion body region, a hemagglutinin gene, a host range region, and a large subunit, ribonucleotide reductase are deleted from the virus; or the poxvirus is a NYVAC recombinant virus; and wherein the exogenous DNA encodes: HIV1 gag(+pro)(IIIB), gp120(MN)(+transmembrane) and two nef(BRU)CTL epitopes; or gp120(MN)(+transmembrane) and two ELDKWA (SEQ ID NO: 147) epitopes in the gp120 V3 loop region; or HIV1 gag(+pro)(IIIB) and gp120(MN)(+transmembrane); or HIV1 gag(+pro)(IIIB), gp120(MN)(+transmembrane) and two nef(BRU) and three pol(IIIB) CTL epitope containing regions; or at least one of: HIV1 gag(+pro)(IIIB), gp120(MN)(+transmembrane), nef(BRU)CTL, pol(IIIB)CTL, and ELDKWA (SEQ ID NO: 147) or LDKW (SEQ ID NO: 148) epitopes.

2. The recombinant poxvirus of claim 1 wherein wherein the exogenous DNA encodes HIV1 gag(+pro)(IIIB), gp120(MN)(+transmembrane) and two nef(BRU)CTL epitopes.

3. The recombinant poxvirus of claim 2 wherein the two nef(BRU)CTL epitopes are CTL1 and CTL2.

4. The recombinant poxvirus of claim 1 wherein the exogenous DNA encodes gp120(MN)(+transmembrane) and two ELDKWA (SEO ID NO: 147) epitopes in the gp120 V3 loop region.

5. The recombinant poxvirus of claim 1 wherein the exogenous DNA encodes HIV1 gag(+pro)(IIIB) and gp120(MN)(+transmembrane).

6. The recombinant poxvirus of claim 1 wherein the exogenous DNA encodes HIV1 gag(+pro)(IIIB), gp120(MN)(+transmembrane) and two nef(BRU) and three pol(IIIB) CTL epitope containing regions.

7. The recombinant poxvirus of claim 6 wherein the two nef(BRU)CTL and three pol(IIIB)CTL epitopes are: CTL1, CTL2, pol1, pol2 and pol3.

8. The recombinant poxvirus of claim 1 which is a NYVAC recombinant virus.

9. The recombinant poxvirus of claim 1 wherein the exogenous DNA codes for at least one of: HIV1 gag(+pro)(IIIB), gp120(MN)(+transmembrane), nef(BRU)CTL, pol(IIIB)CTL, and ELDKWA (SEQ ID NO: 147) or LDKW (SEQ ID NO: 148) epitopes.

10. The recombinant poxvirus of claim 9 wherein the exogenous DNA codes for HIV1 gag(+pro)(IIIB), gp120(MN)(+transmembrane), two nef(BRU)CTL and three pol(IIIB)CTL epitopes; or, two ELDKWA (SEO ID NO: 147) epitopes.

11. The recombinant poxvirus of claim 10 wherein the two nef(BRU)CTL and three pol(IIIB)CTL epitopes are: CTL1, CTL2, pol1, pol2 and pol3.

12. The recombinant poxvirus of claim 9 wherein the ELDKWA (SEQ ID NO: 147) or LDKW (SEQ ID NO: 148) epitopes are expressed as part of a region of gp120 or a region of gp160.

13. The virus of claim 12 wherein the ELDKWA (SEQ ID NO: 147) or LDKW (SEQ ID NO: 148) epitopes are expressed as part of gp120 V3.

14. A recombinant poxvirus which is vP1313.

15. A immunogenic composition comprising a recombinant poxvirus as claimed in claim 1 and a carrier.

16. A method for expressing a Lentivirus gene product comprising infecting a suitable host cell with a recombinant poxvirus as claimed in claim 1.

17. A method for inducing an immunogical response to a Lentivirus gene product comprising administering a recombinant poxvirus as claimed in claim 1.

18. A method for inducing an immunogical response to a Lentivirus gene product comprising administering a composition as claimed in claim 15.

19. A method for inducing an immunogical response to a Lentivirus gene product comprising administering a recombinant poxvirus comprising exogenous DNA encoding at least one Lentivirus epitope, wherein the poxvirus is a vaccinia virus having J2R, B13R+B14R, A26L, A56R, C7L-K1L and I4L are deleted from the virus; or a thymidine kinase gene, a hemorrhagic region, an A type inclusion body region, a hemagglutinin gene, a host range region, and a large subunit, ribonucleotide reductase are deleted from the virus; or the poxvirus is a NYVAC recombinant virus; and said method further comprising subsequently administering an antigen derived from a Lentivirus, whereby the administation of the recombinant poxvirus is a priming administration and the administration of the antigen derived from the Lentivirus is a booster administration.

20. The method of claim 18 further comprising subsequently administering an antigen derived from Lentivirus, whereby the administation of the composition is a priming administration and the administration of the antigen derived from Lentivirus is a booster administration.

21. The method of claim 19 wherein the Lentivirus is human immunodeficiency virus.

22. A recombinant poxvirus which is vP1319.

23. The method of claim 17 further comprising subsequently administering an antigen derived from Lentivirus, whereby the administation of the composition is a priming administration and the administration of the antigen derived from Lentivirus is a booster administration.

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Patent Assignee Address, Country	/PA.CNY
Patent Assignee Address, State	/PA.ST
Patent Assignee Address, ZIP code	/PA.ZIP
Patent Assignee Type	/PAT
Patent Country	/PC
Patent Number	/PN
Patent Kind	/PK
Priority Country	/PRC
Priority Date	/PRD
Priority Number (1)	/PRN
Priority Year	/PRY
Publication Date	/PD
Publication Year	/PY

Reference Non-Patent Information	/RNP
Reference Patent Classification	/RPCL
Reference Patent Country	/RPC
Reference Patent Inventor	/RPIN
Reference Patent IPC	/RPIC
Reference Patent Number	/RPN
Reference Patent Publication Date	/RPD
Reference Patent Publication Year	/RPY
Related Application Country	/RLC
Related Application Date	/RLD
Related Application Number	/RLN
Related Application Year	/RLY
Related Patent Number	/RLPN
Related Patent Publication Year	/RLPY
Related Publication Indicator	/RLP
Section Cross-reference (CA data)	/SX
Supplementary Term (CA data)	/ST
Term of Patent	/PTERM
Title	/TI
Update Date	/UP
Update Date of CA Indexing	/UPCA

(1) US provisional priority numbers are searched only with a P appended, e.g., US1999-121903P/PRN.

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Search Field Name	Super Search Code	Fields Searched
International Patent Classifications	/IPC	/IC, /ICM, /ICS
Patent Application Group	/APPS	/AP, /PRN, /RLN
Patent Country Group	/PCS	/PC, /RPC, /FC
Patent Number Group	/PATS	/PN, /FN, /RPN, /RLPN

(1) This field contains the classifications and catchwords for main classification subject headings and subheadings from the current (7th) edition of the WIPO International Patent Classifications (IPC) manual. To search the classifications from any of the previous editions (1-6) of the IPC manual, use the field code followed by the edition number, e.g., /IC2, ICM2, /ICS2 for the 2nd edition. Catchwords are included only in the fields for the 7th, 6th and 5th editions of the IPC manual.

All fields are text fields except Application Date (/AD), Art Unit (/ARTU), Application Year (/AY), Number of Claims (/CLMN), Disclaimer Date (/DCD), Entry Date (/ED), Inventor Address, ZIP code (/IN.ZIP), Line Count (/LN.CNT), IPC Main Group Range Searchable (/MGR), Patent Assignee Address, ZIP code (/PA.ZIP), Publication Date (/PD), Priority Date (/PRD), Priority Year (/PRY), Term of Patent (/PTERM), Publication Year (/PY), Related Application Date (/RLD), Related Patent Publication Year (/RLPY), Related Application Year (/RLY), Reference Patent Publication Date (/RPD), Reference Patent Publication Year (/RPY), IPC Subgroup Range Searchable (/SGR), Update Date (/UP), and Update Date of CA Indexing (/UPCA which are numeric and may be searched with numeric operators or ranges, e.g., PY> 1992.

International Patent Classification (/IC), International Patent

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  Classification, Main (/ICM), International Patent Classification,
  Secondary (/ICS), National Patent Classification, Issue (/INCL),
  National Patent Classification, Issue, Main (/INCLM), National Patent
  Classification, Issue, Secondary (/INCLS), National Patent
  Classification, Current, (/NCL), National Patent Classification,
  Current, Main (/NCLM), and National Patent Classification, Current,
  Secondary (/NCLS) are range-searchable in the International Patent
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  see a list of display fields, enter HELP DFIELDS at an arrow prompt
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=> e zdenek hel/in
E1            2      ZDENEK GENE/IN
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E12           1      ZDIMAL JOSEPH E/IN

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E15           5      ZDINAK PAUL/IN
E16           4      ZDINAK PAUL S/IN
E17           1      ZDINAK WILLIAM D/IN
E18           1      ZDOBINSKI DAVID B/IN
E19           1      ZDON VLADIMIR A/IN
E20           3      ZDOR GENNADY NIKOLAEVICH/IN
E21           1      ZDOROV IGOR P/IN
E22           1      ZDRAHAL PAVEL/IN
E23           1      ZDRAHAL PETER/IN
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E27           1      ZDRAL JULIAN/IN
E28           5      ZDRALEK JAMES F/IN
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L4             0 GENE SHEARER/IN

=> s shearer gene/in
L5             1 SHEARER GENE/IN

=> d l5,cbib

L5   ANSWER 1 OF 1  USPATFULL on STN
94:68846 Peptides stimulating cytotoxic T cells immune to HIV RT.
     Berzofsky, Jay A., Bethesda, MD, United States
     Hosmalin, Anne, Bethesda, MD, United States
     Clerici, Mario S., Bethesda, MD, United States
     Germain, Ronald N., Potomac, MD, United States
     Shearer, Gene, Bethesda, MD, United States
     Moss, Bernard, Bethesda, MD, United States
     Pendleton, Charles D., Bethesda, MD, United States
     The United States of America as represented by the Department of Health and
     Human Services, Washington, DC, United States (U.S. government)
     US 5336758 19940809
     APPLICATION: US 1990-489825  19900309 (7)
     DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.


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E12            1      SHEARER HERBERT N/IN

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L6             7 "SHEARER GENE M"/IN

=> d l6,ti,1-7

L6   ANSWER 1 OF 7  USPATFULL on STN
TI     Treatment of Kaposi's sarcoma with IL-12

L6   ANSWER 2 OF 7  USPATFULL on STN
TI     Treatment of Kaposi's sarcoma with IL-12

L6   ANSWER 3 OF 7  USPATFULL on STN
TI     Treatment of Kaposi's sarcoma with IL-12

L6   ANSWER 4 OF 7  USPATFULL on STN
TI     Method of inducing cell-mediated protective immunity against HIV using
       low doses of immunogens

L6   ANSWER 5 OF 7  USPATFULL on STN
TI     In vitro methods for assessing the susceptibility of HIV-1-infected
       individuals to cysteine protease-mediated activation-induced programmed
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L6   ANSWER 6 OF 7  USPATFULL on STN
TI      Method for detecting immune dysfunction in asymptomatic aids patients
        and for predicting organ transplant rejection

L6   ANSWER 7 OF 7  USPATFULL on STN
TI      Method for detecting immune system dysfunction in asymptomatic,
        HIV-scropositive individuals


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FULL ESTIMATED COST                                      21.35      21.56

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 FILE LAST UPDATED: 1 APR 2004 (20040401/UP).  FILE COVERS 1951 TO DATE.

 On February 29, 2004, the 2004 MeSH terms were loaded.  See HELP RLOAD
 for details. OLDMEDLINE now back to 1951.

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 http://www.nlm.nih.gov/pubs/techbull/nd03/nd03_mesh.html for a
 description of changes.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

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L7         196 "FRANCHINI G"/AU OR "FRANCHINI GENOVEFFA"/AU

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[illegible] HUMAN
112466 IMMUNODEFICIENCY
372233 VIRUS
42485 HUMAN IMMUNODEFICIENCY VIRUS
(HUMAN(W)IMMUNODEFICIENCY(W)VIRUS)
L8 67 L7 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)

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468149 MAJOR
66178 HISTOCOMPATIBILITY
25318 MAJOR HISTOCOMPATIBILITY
(MAJOR(W)HISTOCOMPATIBILITY)
11061 CTL
81352 CYTOTOXIC
3621943 T
2479333 CELL?
6698 CYTOTOXIC T CELL?
(CYTOTOXIC(W)T(W)CELL?)
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357886 LYMPHOCYTE?
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=> d l9,cbib,1-16

L9 ANSWER 1 OF 16 MEDLINE on STN
2004042570. PubMed ID: 14741150. Avipox-based simian immunodeficiency virus (SIV) vaccines elicit a high frequency of SIV-specific CD4+ and CD8+ T-cell responses in vaccinia-experienced SIVmac251-infected macaques. Nacsa Janos; Radaelli Antonia; Edghill-Smith Yvette; Venzon David; Tsai Wen-Po; Morghen Carlo De Giuli; Panicali Dennis; Tartaglia Jim; **Franchini Genoveffa**. (Basic Research Laboratory, National Cancer Institute, 41/D804 Bethesda, MD 20892-5055, USA.. jn97w@nih.gov) . Vaccine, (2004 Jan 26) 22 (5-6) 597-606. Journal code: 8406899. ISSN: 0264-410X. Pub. country: Netherlands. Language: English.

L9 ANSWER 2 OF 16 MEDLINE on STN
2002742849. PubMed ID: 12504554. Emergence of **cytotoxic T lymphocyte** escape mutants following antiretroviral treatment suspension in rhesus macaques infected with SIVmac251. Nacsa Janos; Stanton Jennifer; Kunstman Kevin J; Tsai Wen Po; Watkins David I; Wolinsky Steven M; **Franchini Genoveffa**. (National Cancer Institute, Basic Research Laboratory, 41/D804, Bethesda, Maryland 20892, USA.) Virology, (2003 Jan 5) 305 (1) 210-8. Journal code: 0110674. ISSN: 0042-6822. Pub. country: United States. Language: English.

L9 ANSWER 3 OF 16 MEDLINE on STN
2002651172. PubMed ID: 12388726. Both mucosal and systemic routes of immunization with the live, attenuated NYVAC/simian immunodeficiency virus SIV(gpe) recombinant vaccine result in gag-specific CD8(+) T-cell responses in mucosal tissues of macaques. Stevceva Liljana; Alvarez Xavier; Lackner Andrew A; Tryniszewska Elzbieta; Kelsall Brian; Nacsa Janos; Tartaglia Jim; Strober Warren; **Franchini Genoveffa**. (Basic Research Laboratory, National Cancer Institute, Bethesda, Maryland 20892, USA.) Journal of virology, (2002 Nov) 76 (22) 11659-76. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

L9 ANSWER 4 OF 16 MEDLINE on STN
2002487223. PubMed ID: 12297331. Retroviral proteins that target the **major histocompatibility** complex class I. Johnson Julie M; **Franchini Genoveffa**. (National Cancer Institute, Basic Research Laboratory, 41/D804, Bethesda, MD 20892-5055, USA.. johnsonjm@helix.nih.gov) . Virus

research, (2002 Sep) 88 (1-2) 119-27. Ref: 80. Journal code: 8410979.
ISSN: 0168-1702. Pub. country: Netherlands. Language: English.

L9 ANSWER 5 OF 16 MEDLINE on STN
2002094227. PubMed ID: 11823518. Recombinant canarypox vaccine-elicited **CTL** specific for dominant and subdominant simian immunodeficiency virus epitopes in rhesus monkeys. Santra Sampa; Schmitz Jorn E; Kuroda Marcelo J; Lifton Michelle A; Nickerson Christine E; Lord Carol I; Pal Ranajit; **Franchini Genoveffa**; Letvin Norman L. (Division of Viral Pathogenesis, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA 02115, USA.) Journal of immunology (Baltimore, Md. : 1950), (2002 Feb 15) 168 (4) 1847-53. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

L9 ANSWER 6 OF 16 MEDLINE on STN
2002046655. PubMed ID: 11752176. Dominance of CD8 responses specific for epitopes bound by a single **major histocompatibility** complex class I molecule during the acute phase of viral infection. Mothe Bianca R; Horton Helen; Carter Donald K; Allen Todd M; Liebl Max E; Skinner Pam; Vogel Thorsten U; Fuenger Sarah; Vielhuber Kathy; Rehrauer William; Wilson Nancy; **Franchini Genoveffa**; Altman John D; Haase Ashley; Picker Louis J; Allison David B; Watkins David I. (Wisconsin Regional Primate Research Center, University of Wisconsin, Madison, Wisconsin 53715, USA.) Journal of virology, (2002 Jan) 76 (2) 875-84. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

L9 ANSWER 7 OF 16 MEDLINE on STN
2001693256. PubMed ID: 11739667. Cervicovaginal lamina propria lymphocytes: phenotypic characterization and their importance in **cytotoxic T-lymphocyte** responses to simian immunodeficiency virus SIVmac251. Stevceva Liljana; Kelsall Brian; Nacsa Janos; Moniuszko Marcin; Hel Zdenek; Tryniszewska Elzbieta; **Franchini Genoveffa**. (Animal Models and Retroviral Vaccines Section, Basic Research Laboratory, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892, USA.) Journal of virology, (2002 Jan) 76 (1) 9-18. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

L9 ANSWER 8 OF 16 MEDLINE on STN
2001693250. PubMed ID: 11739694. ALVAC-SIV-gag-pol-env-based vaccination and macaque **major histocompatibility** complex class I (A*01) delay simian immunodeficiency virus SIVmac-induced immunodeficiency. Pal R; Venzon D; Letvin N L; Santra S; Montefiori D C; Miller N R; Tryniszewska E; Lewis M G; VanCott T C; Hirsch V; Woodward R; Gibson A; Grace M; Dobratz E; Markham P D; Hel Z; Nacsa J; Klein M; Tartaglia J; **Franchini G**. (Advanced BioScience Laboratories, Inc., Kensington, Maryland 20895, USA.) Journal of virology, (2002 Jan) 76 (1) 292-302. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

L9 ANSWER 9 OF 16 MEDLINE on STN
2001680659. PubMed ID: 11726972. Mucosal AIDS vaccine reduces disease and viral load in gut reservoir and blood after mucosal infection of macaques. Belyakov I M; Hel Z; Kelsall B; Kuznetsov V A; Ahlers J D; Nacsa J; Watkins D I; Allen T M; Sette A; Altman J; Woodward R; Markham P D; Clements J D; **Franchini G**; Strober W; Berzofsky J A. (Molecular Immunogenetics and Vaccine Research Section, Metabolism Branch, National Cancer Institute, Bethesda, Maryland, USA.. belyakov@box-b.nih.gov) . Nature medicine, (2001 Dec) 7 (12) 1320-6. Journal code: 9502015. ISSN: 1078-8956. Pub. country: United States. Language: English.

L9 ANSWER 10 OF 16 MEDLINE on STN
2001639968. PubMed ID: 11689630. Impairment of Gag-specific CD8(+) T-cell function in mucosal and systemic compartments of simian immunodeficiency virus mac251- and simian-**human immunodeficiency virus** KU2-infected macaques. Hel Z; Nacsa J; Kelsall B; Tsai W P; Letvin N; Parks R W; Tryniszewska E; Picker L; Lewis M G; Edghill-Smith Y; Moniuszko M; Pal R; Stevceva L; Altman J D; Allen T M; Watkins D; Torres J V; Berzofsky J A;

Belyakov I M; Strober W; **Franchini G**. (Basic Research Laboratory,
Bethesda, Maryland 20892, USA.) Journal of virology, (2001 Dec) 75 (23) 11483-95. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

L9 ANSWER 11 OF 16 MEDLINE on STN
2001338261. PubMed ID: 11101054. Cross-protection in NYVAC-**HIV**-1-immunized/**HIV**-2-challenged but not in NYVAC-**HIV**-2-immunized/SHIV-challenged rhesus macaques. Patterson L J; Peng B; Abimiku A G; Aldrich K; Murty L; Markham P D; Kalyanaraman V S; Alvord W G; Tartaglia J; **Franchini G**; Robert-Guroff M. (Basic Research Laboratory, National Cancer Institute, Bethesda, Maryland 20892-5055, USA.) AIDS (London, England), (2000 Nov 10) 14 (16) 2445-55. Journal code: 8710219. ISSN: 0269-9370. Pub. country: ENGLAND: United Kingdom. Language: English.

L9 ANSWER 12 OF 16 MEDLINE on STN
2000459431. PubMed ID: 10954578. **Human immunodeficiency virus** type 1 envelope epitope-specific CD4(+) T lymphocytes in simian/**human immunodeficiency virus**-infected and vaccinated rhesus monkeys detected using a peptide-**major histocompatibility** complex class II tetramer. Kuroda M J; Schmitz J E; Lekutis C; Nickerson C E; Lifton M A; **Franchini G**; Harouse J M; Cheng-Mayer C; Letvin N L. (Division of Viral Pathogenesis, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts 02215, USA.. mkuroda@caregroup.harvard.edu) . Journal of virology, (2000 Sep) 74 (18) 8751-6. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

L9 ANSWER 13 OF 16 MEDLINE on STN
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L9 ANSWER 14 OF 16 MEDLINE on STN
97051863. PubMed ID: 8896498. Immunogenicity and protective efficacy of a **human immunodeficiency virus** type 2 recombinant canarypox (ALVAC) vaccine candidate in cynomolgus monkeys. Andersson S; Makitalo B; Thorstensson R; **Franchini G**; Tartaglia J; Limbach K; Paoletti E; Putkonen P; Biberfeld G. (Swedish Institute for Infectious Disease Control, Stockholm, Sweden.) Journal of infectious diseases, (1996 Nov) 174 (5) 977-85. Journal code: 0413675. ISSN: 0022-1899. Pub. country: United States. Language: English.

L9 ANSWER 15 OF 16 MEDLINE on STN
96424753. PubMed ID: 8827214. Multiple immunizations with attenuated poxvirus **HIV** type 2 recombinants and subunit boosts required for protection of rhesus macaques. Myagkikh M; Alipanah S; Markham P D; Tartaglia J; Paoletti E; Gallo R C; **Franchini G**; Robert-Guroff M. (Laboratory of Tumor Cell Biology, DBS, NCI, NIH, Bethesda, Maryland 20892-4255, USA.) AIDS research and human retroviruses, (1996 Jul 20) 12 (11) 985-92. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

L9 ANSWER 16 OF 16 MEDLINE on STN
95306142. PubMed ID: 7786583. Humoral and cellular immune responses in rhesus macaques infected with **human immunodeficiency virus** type 2. Abimiku A G; **Franchini G**; Aldrich K; Myagkikh M; Markham P; Gard E; Gallo R C; Robert-Guroff M. (Laboratory of Tumor Cell Biology, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892, USA.) AIDS research and human retroviruses, (1995 Mar) 11 (3) 383-93. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States.

Language: English.

=> d l9,cbib,ab,4,6

L9 ANSWER 4 OF 16 MEDLINE on STN
2002487223. PubMed ID: 12297331. Retroviral proteins that target the **major histocompatibility** complex class I. Johnson Julie M; **Franchini Genoveffa**. (National Cancer Institute, Basic Research Laboratory, 41/D804, Bethesda, MD 20892-5055, USA.. johnsonjm@helix.nih.gov) . Virus research, (2002 Sep) 88 (1-2) 119-27. Ref: 80. Journal code: 8410979. ISSN: 0168-1702. Pub. country: Netherlands. Language: English.

AB The human T-cell leukemia virus type 1 (HTLV-1) and **human immunodeficiency virus** type 1 (**HIV**-1) retroviruses are two evolutionary distinct human pathogens. HTLV-1 is the etiologic agent of two diverse diseases: adult T-cell leukemia/lymphoma, as well as the neurologic disorder tropical spastic paraparesis/HTLV-1-associated myelopathy. HTLV-1 is the only retrovirus known to be the etiologic agent of human cancer. HTLV-2, the other known oncovirus, is not apparently associated with human cancer. While HTLV-1 transforms T-cells in vitro, **HIV** kills CD4+ T-cells and is the etiological agent of human acquired immunodeficiency syndrome, characterized by a progressive loss of CD4+ cells, weakening of the immune system, and susceptibility to opportunistic infections and cancer. HTLV-1 and **HIV**-1 both cause lifelong infections, which suggests that they have evolved mechanism(s) to evade detection by the host's immune response; particularly to evade **cytotoxic T-lymphocytes**, which play a major role in cellular immunity against viruses and will be the focus of this review.

L9 ANSWER 6 OF 16 MEDLINE on STN
2002046655. PubMed ID: 11752176. Dominance of CD8 responses specific for epitopes bound by a single **major histocompatibility** complex class I molecule during the acute phase of viral infection. Mothe Bianca R; Horton Helen; Carter Donald K; Allen Todd M; Liebl Max E; Skinner Pam; Vogel Thorsten U; Fuenger Sarah; Vielhuber Kathy; Rehrauer William; Wilson Nancy; **Franchini Genoveffa**; Altman John D; Haase Ashley; Picker Louis J; Allison David B; Watkins David I. (Wisconsin Regional Primate Research Center, University of Wisconsin, Madison, Wisconsin 53715, USA.) Journal of virology, (2002 Jan) 76 (2) 875-84. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB **Cytotoxic T-lymphocyte** (**CTL**) responses are thought to control **human immunodeficiency virus** replication during the acute phase of infection. Understanding the CD8(+) T-cell immune responses early after infection may, therefore, be important to vaccine design. Analyzing these responses in humans is difficult since few patients are diagnosed during early infection. Additionally, patients are infected by a variety of viral subtypes, making it hard to design reagents to measure their acute-phase immune responses. Given the complexities in evaluating acute-phase CD8(+) responses in humans, we analyzed these important immune responses in rhesus macaques expressing a common rhesus macaque **major histocompatibility** complex class I molecule (Mamu-A*01) for which we had developed a variety of immunological assays. We infected eight Mamu-A*01-positive macaques and five Mamu-A*01-negative macaques with the molecularly cloned virus SIV(mac)239 and determined all of the simian immunodeficiency virus-specific CD8(+) T-cell responses against overlapping peptides spanning the entire virus. We also monitored the evolution of particular CD8(+) T-cell responses by tetramer staining of peripheral lymphocytes as well as lymph node cells in situ. In this first analysis of the entire CD8(+) immune response to autologous virus we show that between 2 and 12 responses are detected during the acute phase in each animal. **CTL** against the early proteins (Tat, Rev, and Nef) and against regulatory proteins Vif and Vpr dominated the acute phase. Interestingly, CD8(+) responses against Mamu-A*01-restricted epitopes Tat(28-35)SL8 and Gag(181-189)CM9 were immunodominant in the acute phase. After the acute phase, however, this pattern of reactivity changed, and the Mamu-A*01-restricted response against the Gag(181-189)CM9 epitope

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became dominant. In most of the Mamu-A*01 positive macaques tested, CTL
     responses against epitopes bound by Mamu-A*01 dominated the CD8(+)
     cellular immune response.


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L4            0 S GENE SHEARER/IN
L5            1 S SHEARER GENE/IN
                E SHEARER GENE/IN
L6            7 S E4
                E NACSA JANOS/IN

     FILE 'MEDLINE' ENTERED AT 19:47:38 ON 01 APR 2004
                E FRANCHINI G/AU
L7          196 S E3 OR E4
L8           67 S L7 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L9           16 S L8 AND (MHC OR MAJOR HISTOCOMPATIBILITY OR CTL OR CYTOTOXIC T

=> e hel z/au
You may either continue the previous EXPAND listing or
start a new list.  To continue, take the default.  To start
a new EXPAND list, enter a term.
E13           1      FRANCHINI LAURA/AU
E14           1      FRANCHINI LUCIA F/AU
E15          84      FRANCHINI M/AU
E16           2      FRANCHINI M A/AU
E17           5      FRANCHINI M I/AU
E18           3      FRANCHINI M K/AU
E19           4      FRANCHINI MARCO/AU
E20           1      FRANCHINI MARIA LUISA/AU
E21           1      FRANCHINI MARIELLA/AU
E22          23      FRANCHINI MASSIMO/AU
E23           2      FRANCHINI MICHELA/AU
E24           1      FRANCHINI MIRELLA/AU

=> s hel z/au
Enter the terms you wish to use in your search profile.
ENTER LOGIC EXPRESSION, QUERY NAME, OR (END):s hel z/au
L10           0 S HEL Z/AU

=> e hel z/au
You may either continue the previous EXPAND listing or
start a new list.  To continue, take the default.  To start
a new EXPAND list, enter a term.
E25           2      FRANCHINI N/AU
E26           7      FRANCHINI P/AU
E27           2      FRANCHINI P L/AU
E28           1      FRANCHINI PATRICK L/AU
E29          13      FRANCHINI R/AU
E30           2      FRANCHINI RAMIRES J A/AU
E31           1      FRANCHINI RAMIRES J A A/AU
E32           2      FRANCHINI RAMIRES JOSE ANTONIO/AU
E33           9      FRANCHINI S/AU
E34           2      FRANCHINI SILVIA/AU
E35           1      FRANCHINI T/AU
E36          19      FRANCHINI V/AU
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=> e shearer g m/au
E1          10     SHEARER G JR/AU
E2           3     SHEARER G L/AU
E3         349 --> SHEARER G M/AU
E4           4     SHEARER G O/AU
E5           3     SHEARER G R/AU
E6           1     SHEARER GENE/AU
E7           8     SHEARER GENE M/AU
E8           1     SHEARER GEORGIA/AU
E9           1     SHEARER GLENMORE JR/AU
E10          1     SHEARER GREGORY C/AU
E11          1     SHEARER H/AU
E12          3     SHEARER H H/AU

=> s e3 or e6 or e7
           349 "SHEARER G M"/AU
             1 "SHEARER GENE"/AU
             8 "SHEARER GENE M"/AU
L11        358 "SHEARER G M"/AU OR "SHEARER GENE"/AU OR "SHEARER GENE M"/AU

=> s l11 and (HIV or human immunodeficiency virus)
        135256 HIV
       8464764 HUMAN
        112466 IMMUNODEFICIENCY
        372233 VIRUS
         42485 HUMAN IMMUNODEFICIENCY VIRUS
                 (HUMAN(W)IMMUNODEFICIENCY(W)VIRUS)
L12        118 L11 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)

=> s l12 and (major histocompatibility or CTL or cytotoxic)
        468149 MAJOR
         66178 HISTOCOMPATIBILITY
         25318 MAJOR HISTOCOMPATIBILITY
                 (MAJOR(W)HISTOCOMPATIBILITY)
         11061 CTL
         81352 CYTOTOXIC
L13         20 L12 AND (MAJOR HISTOCOMPATIBILITY OR CTL OR CYTOTOXIC)

=> d l13,cbib,1-20
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L13 ANSWER 1 OF 20 MEDLINE on STN
2002637310. PubMed ID: 12396457. Immunologic profile of highly exposed yet **HIV** type 1-seronegative men. Yang Otto O; Boscardin W John; Matud Jose; Hausner Mary Ann; Hultin Lance E; Hultin Patricia M; Shih Roger; Ferbas John; Siegal Frederick P; Shodell Michael; **Shearer Gene M**; Grene Edith; Carrington Mary; O'Brien Steve; Price Charles B; Detels Roger; Jamieson Beth D; Giorgi Janis V. (Department of Medicine, UCLA Medical Center, Los Angeles, California 90095, USA.) AIDS research and human retroviruses, (2002 Sep 20) 18 (14) 1051-65. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

L13 ANSWER 2 OF 20 MEDLINE on STN
2001200939. PubMed ID: 11118074. T cell responses to recall antigens, alloantigen, and mitogen of **HIV**-infected patients receiving long-term combined antiretroviral therapy. Blazevic V; Sahgal N; Kessler H A; Landay A L; **Shearer G M**. (Experimental Immunology Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892, USA.) AIDS research and human retroviruses, (2000 Nov 20) 16 (17) 1887-93. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

L13 ANSWER 3 OF 20 MEDLINE on STN
2001137034. PubMed ID: 11114968. **HIV**-1-specific cellular immune responses among **HIV**-1-resistant sex workers. Fowke K R; Kaul R; Rosenthal K L; Oyugi J; Kimani J; Rutherford W J; Nagelkerke N J; Ball T B; Bwayo J J; Simonsen J N; **Shearer G M**; Plummer F A. (Department of

Medical Microbiology, University of Manitoba, Winnipeg, Canada.. fowkekr@cc.umanitoba.ca) . Immunology and cell biology, (2000 Dec) 78 (6) 586-95. Journal code: 8706300. ISSN: 0818-9641. Pub. country: Australia. Language: English.

L13 ANSWER 4 OF 20 MEDLINE on STN
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L13 ANSWER 5 OF 20 MEDLINE on STN
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L13 ANSWER 6 OF 20 MEDLINE on STN
2000012343. PubMed ID: 10546852. **HIV**-specific immunity following immunization with **HIV** synthetic envelope peptides in asymptomatic **HIV**-infected patients. Pinto L A; Berzofsky J A; Fowke K R; Little R F; Merced-Galindez F; Humphrey R; Ahlers J; Dunlop N; Cohen R B; Steinberg S M; Nara P; **Shearer G M**; Yarchoan R. (Experimental Immunology Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892, USA.) AIDS (London, England), (1999 Oct 22) 13 (15) 2003-12. Journal code: 8710219. ISSN: 0269-9370. Pub. country: ENGLAND: United Kingdom. Language: English.

L13 ANSWER 7 OF 20 MEDLINE on STN
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L13 ANSWER 8 OF 20 MEDLINE on STN
1999059625. PubMed ID: 9845492. Immune response to **human immunodeficiency virus** (**HIV**) in healthcare workers occupationally exposed to **HIV**-contaminated blood. Pinto L A; Landay A L; Berzofsky J A; Kessler H A; **Shearer G M**. (Experimental Immunology Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892, USA.) American journal of medicine, (1997 May 19) 102 (5B) 21-4. Ref: 31. Journal code: 0267200. ISSN: 0002-9343. Pub. country: United States. Language: English.

L13 ANSWER 9 OF 20 MEDLINE on STN
97048211. PubMed ID: 8893047. Mother-to-infant transmission of **HIV** type 1: role of **major histocompatibility** antigen differences. Mittleman B B; **Shearer G M**. (Experimental Immunology Branch, National Cancer Institute/NIH, Bethesda, Maryland 20892, USA.) AIDS research and human retroviruses, (1996 Oct 10) 12 (15) 1397-400. Ref: 38. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

L13 ANSWER 10 OF 20 MEDLINE on STN
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have antibodies to HLA class I antigens and T cells specific for **HIV**
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Quirinale J; Cosma A; Robbioni P; **Shearer G M**; Berzofsky J A; +.
(Department of Biology and Technology, S. Raffaele Scientific Institute,
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Journal code: 0413675. ISSN: 0022-1899. Pub. country: United States.
Language: English.

L13 ANSWER 11 OF 20 MEDLINE on STN
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responses in **HIV** seronegative health care workers occupationally exposed
to **HIV**-contaminated body fluids. Pinto L A; Sullivan J; Berzofsky J A;
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investigation, (1995 Aug) 96 (2) 867-76. Journal code: 7802877. ISSN:
0021-9738. Pub. country: United States. Language: English.

L13 ANSWER 12 OF 20 MEDLINE on STN
93262483. PubMed ID: 8098553. A strategy for prophylactic vaccination
against **HIV**. Salk J; Bretscher P A; Salk P L; Clerici M; **Shearer G M.**
(Salk Institute for Biological Studies, San Diego, CA 92138.) Science,
(1993 May 28) 260 (5112) 1270-2. Journal code: 0404511. ISSN: 0036-8075.
Pub. country: United States. Language: English.

L13 ANSWER 13 OF 20 MEDLINE on STN
92064980. PubMed ID: 1720151. **Human immunodeficiency virus** reverse
transcriptase T helper epitopes identified in mice and humans: correlation
with a **cytotoxic** T cell epitope. De Groot A S; Clerici M; Hosmalin A;
Hughes S H; Barnd D; Hendrix C W; Houghten R; **Shearer G M**; Berzofsky J
A. (Molecular Immunogenetics and Vaccine Research Section, National Cancer
Institute, National Institutes of Health, Bethesda, Maryland 20892.)
Journal of infectious diseases, (1991 Dec) 164 (6) 1058-65. Journal code:
0413675. ISSN: 0022-1899. Pub. country: United States. Language: English.

L13 ANSWER 14 OF 20 MEDLINE on STN
91184274. PubMed ID: 1672645. Functional dichotomy of CD4+ T helper
lymphocytes in asymptomatic **human immunodeficiency virus** infection.
Clerici M; Via C S; Lucey D R; Roilides E; Pizzo P A; **Shearer G M.**
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English.

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specific for synthetic peptides of gp160 in **HIV**-seropositive
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Apr 1) 146 (7) 2214-9. Journal code: 2985117R. ISSN: 0022-1767. Pub.
country: United States. Language: English.

L13 ANSWER 16 OF 20 MEDLINE on STN
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function in **HIV**-infected individuals by stimulation with HLA
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Shearer G M. (Experimental Immunology Branch, National Cancer Institute,
National Institutes of Health, Bethesda, MD 20892.) Journal of immunology
(Baltimore, Md. : 1950), (1990 May 1) 144 (9) 3266-71. Journal code:
2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

L13 ANSWER 17 OF 20 MEDLINE on STN

90192004. PubMed ID: 1690429. An epitope in **human immunodeficiency virus** 1 reverse transcriptase recognized by both mouse and human **cytotoxic** T lymphocytes. Hosmalin A; Clerici M; Houghten R; Pendleton C D; Flexner C; Lucey D R; Moss B; Germain R N; **Shearer G M**; Berzofsky J A. (Metabolism Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892.) Proceedings of the National Academy of Sciences of the United States of America, (1990 Mar) 87 (6) 2344-8. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

L13 ANSWER 18 OF 20 MEDLINE on STN
89024305. PubMed ID: 3263071. Suppression of human **cytotoxic** T lymphocyte responses by adherent peripheral blood leukocytes. Bernstein D C; **Shearer G M**. (Immunology Branch, National Cancer Institute, Bethesda, Maryland 20892.) Annals of the New York Academy of Sciences, (1988) 532 207-13. Journal code: 7506858. ISSN: 0077-8923. Pub. country: United States. Language: English.

L13 ANSWER 19 OF 20 MEDLINE on STN
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L13 ANSWER 20 OF 20 MEDLINE on STN
87009907. PubMed ID: 3489767. A model for the selective loss of **major histocompatibility** complex self-restricted T cell immune responses during the development of acquired immune deficiency syndrome (AIDS). **Shearer G M**; Bernstein D C; Tung K S; Via C S; Redfield R; Salahuddin S Z; Gallo R C. Journal of immunology (Baltimore, Md. : 1950), (1986 Oct 15) 137 (8) 2514-21. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

=> d l13,cbib,ab,6,12

L13 ANSWER 6 OF 20 MEDLINE on STN
2000012343. PubMed ID: 10546852. **HIV**-specific immunity following immunization with **HIV** synthetic envelope peptides in asymptomatic **HIV**-infected patients. Pinto L A; Berzofsky J A; Fowke K R; Little R F; Merced-Galindez F; Humphrey R; Ahlers J; Dunlop N; Cohen R B; Steinberg S M; Nara P; **Shearer G M**; Yarchoan R. (Experimental Immunology Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892, USA.) AIDS (London, England), (1999 Oct 22) 13 (15) 2003-12. Journal code: 8710219. ISSN: 0269-9370. Pub. country: ENGLAND: United Kingdom. Language: English.

AB OBJECTIVE: A phase I trial was conducted to evaluate the safety and immunogenicity of an **HIV** synthetic peptide vaccine in **HIV**-seropositive individuals. The immunogens used in this study were PCLUS 3-18MN and PCLUS 6.1-18MN envelope peptides. METHODS: Eight **HIV**-infected patients received six subcutaneous injections of 160 microg PCLUS 3-18MN in Montanide ISA 51 and were followed longitudinally for a year after the first immunization. Peripheral blood mononuclear cells (PBMC) were tested for peptide-specific T helper and **cytotoxic** T cell (**CTL**) responses, **HIV**-1MN neutralizing antibodies and antibodies against **HIV** PCLUS 3 and P18 MN peptides. RESULTS: PCLUS 3-1 8MN-specific T helper responses were significantly increased at 36 weeks ($P < 0.05$, after adjustment for multiple comparisons) following initial immunization with PCLUS 3-18MN. A P18MN-specific **CTL** response, not present prior to vaccination, was observed after immunization in one patient. Serum **HIV**-1 MN-neutralizing antibody titers increased in each of the three patients who had low titers prior to immunization. Plasma **HIV** RNA levels and CD4 cell counts did not change appreciably during the study period. CONCLUSIONS: This trial

demonstrates that both peptides can be safely administered to **HIV**-infected individuals and that PCLUS 3-18MN induces increases in **HIV** peptide-specific immune responses.

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L13  ANSWER 12 OF 20     MEDLINE on STN
93262483.    PubMed ID: 8098553.   A strategy for prophylactic vaccination
     against HIV. Salk J; Bretscher P A; Salk P L; Clerici M; Shearer G M.
     (Salk Institute for Biological Studies, San Diego, CA 92138. ) Science,
     (1993 May 28) 260 (5112) 1270-2. Journal code: 0404511. ISSN: 0036-8075.
     Pub. country: United States. Language: English.


=> e nacsa j/au
E1            3     NACRY P/AU
E2            2     NACRY PHILIPPE/AU
E3           11 --> NACSA J/AU
E4           11     NACSA JANOS/AU
E5            1     NACSA L/AU
E6            1     NACSA M/AU
E7            1     NACSADI B/AU
E8            2     NACSAI I/AU
E9            2     NACSON J/AU
E10           2     NACSON S/AU
E11           2     NACSON SABATINO/AU
E12           2     NACTEV P/AU

=> s e3 or e4
             11 "NACSA J"/AU
             11 "NACSA JANOS"/AU
L14          22 "NACSA J"/AU OR "NACSA JANOS"/AU

=> d l14,ti,1-22

L14  ANSWER 1 OF 22     MEDLINE on STN
TI   Avipox-based simian immunodeficiency virus (SIV) vaccines elicit a high
     frequency of SIV-specific CD4+ and CD8+ T-cell responses in
     vaccinia-experienced SIVmac251-infected macaques.

L14  ANSWER 2 OF 22     MEDLINE on STN
TI   Modeling a safer smallpox vaccination regimen, for human immunodeficiency
     virus type 1-infected patients, in immunocompromised macaques.

L14  ANSWER 3 OF 22     MEDLINE on STN
TI   Prior DNA immunization enhances immune response to dominant and
     subdominant viral epitopes induced by a fowlpox-based SIVmac vaccine in
     long-term slow-progressor macaques infected with SIVmac251.

L14  ANSWER 4 OF 22     MEDLINE on STN
TI   Human immunodeficiency virus type-1 Tat/co-activator acetyltransferase
     interactions inhibit p53Lys-320 acetylation and p53-responsive
     transcription.

L14  ANSWER 5 OF 22     MEDLINE on STN
TI   Emergence of cytotoxic T lymphocyte escape mutants following
     antiretroviral treatment suspension in rhesus macaques infected with
     SIVmac251.

L14  ANSWER 6 OF 22     MEDLINE on STN
TI   Equivalent immunogenicity of the highly attenuated poxvirus-based
     ALVAC-SIV and NYVAC-SIV vaccine candidates in SIVmac251-infected macaques.

L14  ANSWER 7 OF 22     MEDLINE on STN
TI   Immune intervention strategies for HIV-1 infection of humans in the SIV
     macaque model.

L14  ANSWER 8 OF 22     MEDLINE on STN
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TI Both mucosal and systemic routes of immunization with the live, attenuated NYVAC/simian immunodeficiency virus SIV(gpe) recombinant vaccine result in gag-specific CD8(+) T-cell responses in mucosal tissues of macaques.

L14 ANSWER 9 OF 22 MEDLINE on STN
TI Vaccination of macaques with long-standing SIVmac251 infection lowers the viral set point after cessation of antiretroviral therapy.

L14 ANSWER 10 OF 22 MEDLINE on STN
TI Containment of simian immunodeficiency virus infection in vaccinated macaques: correlation with the magnitude of virus-specific pre- and postchallenge CD4+ and CD8+ T cell responses.

L14 ANSWER 11 OF 22 MEDLINE on STN
TI Differences in time of virus appearance in the blood and virus-specific immune responses in intravenous and intrarectal primary SIVmac251 infection of rhesus macaques; a pilot study.

L14 ANSWER 12 OF 22 MEDLINE on STN
TI Potentiation of simian immunodeficiency virus (SIV)-specific CD4(+) and CD8(+) T cell responses by a DNA-SIV and NYVAC-SIV prime/boost regimen.

L14 ANSWER 13 OF 22 MEDLINE on STN
TI Cervicovaginal lamina propria lymphocytes: phenotypic characterization and their importance in cytotoxic T-lymphocyte responses to simian immunodeficiency virus SIVmac251.

L14 ANSWER 14 OF 22 MEDLINE on STN
TI ALVAC-SIV-gag-pol-env-based vaccination and macaque major histocompatibility complex class I (A*01) delay simian immunodeficiency virus SIVmac-induced immunodeficiency.

L14 ANSWER 15 OF 22 MEDLINE on STN
TI Mucosal AIDS vaccine reduces disease and viral load in gut reservoir and blood after mucosal infection of macaques.

L14 ANSWER 16 OF 22 MEDLINE on STN
TI Impairment of Gag-specific CD8(+) T-cell function in mucosal and systemic compartments of simian immunodeficiency virus mac251- and simian-human immunodeficiency virus KU2-infected macaques.

L14 ANSWER 17 OF 22 MEDLINE on STN
TI Toxoplasma infection and cell free extract of the parasites are able to reverse multidrug resistance of mouse lymphoma and human gastric cancer cells in vitro.

L14 ANSWER 18 OF 22 MEDLINE on STN
TI The inhibition of SOS-responses and MDR by phenothiazine-metal complexes.

L14 ANSWER 19 OF 22 MEDLINE on STN
TI Trifluoperazine and its metal complexes inhibit the Moloney leukemia virus reverse transcriptase.

L14 ANSWER 20 OF 22 MEDLINE on STN
TI Drug resistance reversal, anti-mutagenicity and antiretroviral effect of phthalimido- and chloroethyl-phenothiazines.

L14 ANSWER 21 OF 22 MEDLINE on STN
TI The primary in vitro antitumor screening of "half-mustard type" phenothiazines.

L14 ANSWER 22 OF 22 MEDLINE on STN
TI Reversal of multidrug resistance by amitriptyline in vitro.

=> d his

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     (FILE 'HOME' ENTERED AT 19:42:02 ON 01 APR 2004)

     FILE 'USPATFULL' ENTERED AT 19:42:32 ON 01 APR 2004
                E FRANCHINI GENOVEFFA/IN
L1            7 S E3
L2            0 S ZDENEK HEL/IN
                E ZDENEK HEL/IN
L3            0 S HEL ZDENEK/IN S HEL ZDENEK/IN
L4            0 S GENE SHEARER/IN
L5            1 S SHEARER GENE/IN
                E SHEARER GENE/IN
L6            7 S E4
                E NACSA JANOS/IN

     FILE 'MEDLINE' ENTERED AT 19:47:38 ON 01 APR 2004
                E FRANCHINI G/AU
L7          196 S E3 OR E4
L8           67 S L7 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L9           16 S L8 AND (MHC OR MAJOR HISTOCOMPATIBILITY OR CTL OR CYTOTOXIC T
L10           0 S HEL Z/AU S HEL Z/AU
                E SHEARER G M/AU
L11         358 S E3 OR E6 OR E7
L12         118 S L11 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L13          20 S L12 AND (MAJOR HISTOCOMPATIBILITY OR CTL OR CYTOTOXIC)
                E NACSA J/AU
L14          22 S E3 OR E4

=> file wpids
COST IN U.S. DOLLARS                                  SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                        15.69      37.25

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MOST RECENT DERWENT UPDATE:      200422         <200422/DW>
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=> e franchini g/in
E1            4     FRANCHINI E/IN
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E2            7       FRANCHINI E/IN
E3           18 -->   FRANCHINI G/IN
E4            5       FRANCHINI G C/IN
E5            2       FRANCHINI I/IN
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E7            2       FRANCHINI L A/IN
E8           18       FRANCHINI M/IN
E9            1       FRANCHINI M A/IN
E10           2       FRANCHINI M K/IN
E11           2       FRANCHINI P/IN
E12           1       FRANCHINI P L/IN

=> s e3
L15          18 "FRANCHINI G"/IN

=> s l15 and (HIV or human immunodeficiency virus)
         17388 HIV
        142149 HUMAN
          6711 IMMUNODEFICIENCY
         34785 VIRUS
          4455 HUMAN IMMUNODEFICIENCY VIRUS
                 (HUMAN(W)IMMUNODEFICIENCY(W)VIRUS)
L16          10 L15 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)

=> d l16,bib,1-10

L16  ANSWER 1 OF 10  WPIDS  COPYRIGHT 2004 THOMSON DERWENT on STN
Full Text
AN   2004-192066 [18]   WPIDS
DNC  C2004-075766
TI   Identifying a compound for breaking retroviral latency in a subject,
     useful for identifying compounds for treating retroviral (especially
     HTLV-1 and HIV) infection.
DC   B04 D16
IN   FRANCHINI, G; NICOT, C
PA   (USSH) US DEPT HEALTH & HUMAN SERVICES
CYC  105
PI   WO 2004016228 A2 20040226 (200418)* EN   32p
        RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS
            LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
         W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK
            DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR
            KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH
            PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC
            VN YU ZA ZM ZW
ADT  WO 2004016228 A2 WO 2003-US25958 20030819
PRAI US 2002-404580P  20020819

L16  ANSWER 2 OF 10  WPIDS  COPYRIGHT 2004 THOMSON DERWENT on STN
Full Text
AN   2003-559090 [52]   WPIDS
DNC  C2003-150696
TI   New chimeric rev, tat and nef polypeptide or genes, useful for inducing an
     immune response, or as vaccines for preventing and/or attenuating human
     immunodeficiency virus (HIV) infection.
DC   B04 D16
IN   FRANCHINI, G; HEL, Z; TARTAGLIA, J
PA   (AVET) AVENTIS PASTEUR; (USSH) US DEPT HEALTH & HUMAN SERVICES
CYC  102
PI   WO 2003053338 A2 20030703 (200352)* EN   48p
        RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU
            MC MW MZ NL OA PT SD SE SK SL SZ TR TZ UG ZM ZW
         W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK
            DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR
            KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT
            RO RU SC SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU
```

ZA ZM ZW
ADT WO 2003053338 A2 WO 2002-US36805 20021115
PRAI US 2001-332433P 20011116

L16 ANSWER 3 OF 10 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
Full Text
AN 2002-017728 [02] WPIDS
DNC C2002-005173
TI Vaccinating humans against **Human Immunodeficiency Virus**-1 (**HIV**-1) infection using a combination of nucleic acids encoding **HIV**-1 antigens and recombinant pox viruses to potentiate the immune response.
DC B04 D16
IN **FRANCHINI, G**; HEL, Z; PAVLAKIS, G; TARTAGLIA, J
PA (USSH) US DEPT HEALTH & HUMAN SERVICES; (FRAN-I) FRANCHINI G; (HELZ-I) HEL Z; (PAVL-I) PAVLAKIS G
CYC 96
PI WO 2001082964 A1 20011108 (200202)* EN 37p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2001059291 A 20011112 (200222)
EP 1278541 A1 20030129 (200310) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
JP 2003531865 W 20031028 (200373) 47p
US 2004033237 A1 20040219 (200414)
ADT WO 2001082964 A1 WO 2001-US13968 20010430; AU 2001059291 A AU 2001-59291 20010430; EP 1278541 A1 EP 2001-932792 20010430, WO 2001-US13968 20010430; JP 2003531865 W JP 2001-579837 20010430, WO 2001-US13968 20010430; US 2004033237 A1 WO 2001-US13968 20010430, US 2002-258570 20021025
FDT AU 2001059291 A Based on WO 2001082964; EP 1278541 A1 Based on WO 2001082964; JP 2003531865 W Based on WO 2001082964
PRAI US 2000-200444P 20000428; US 2002-258570 20021025

L16 ANSWER 4 OF 10 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
Full Text
AN 2001-343019 [36] WPIDS
DNC C2001-106103
TI Stimulating CD8(+) response in retrovirus-infected human, involves administering nucleic acid-based vaccine to produce retrovirus specific peptides for cell MHC class I molecules.
DC B04 D16
IN **FRANCHINI, G**; HEL, Z; NACSA, J; SHEARER, G; TARTAGLIA, J
PA (USSH) US DEPT HEALTH & HUMAN SERVICES
CYC 95
PI WO 2001008702 A2 20010208 (200136)* EN 37p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2000066128 A 20010219 (200136)
EP 1198248 A2 20020424 (200235) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
JP 2003505516 W 20030212 (200321) 59p
ADT WO 2001008702 A2 WO 2000-US20641 20000727; AU 2000066128 A AU 2000-66128 20000727; EP 1198248 A2 EP 2000-953728 20000727, WO 2000-US20641 20000727; JP 2003505516 W WO 2000-US20641 20000727, JP 2001-513432 20000727
FDT AU 2000066128 A Based on WO 2001008702; EP 1198248 A2 Based on WO 2001008702; JP 2003505516 W Based on WO 2001008702
PRAI US 2000-200445P 20000428; US 1999-146240P 19990728; US 2000-178989P

L16 ANSWER 5 OF 10 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
Full Text
AN 1999-152779 [13] WPIDS
CR 1991-346752 [47]; 1997-011206 [01]
DNC C1999-045001
TI DNA encoding env protein of the human immune deficiency virus isolate BA-L - useful for producing protein for use in vaccines, as assay reagent and to generate antibodies.
DC B04 D16
IN **FRANCHINI, G**; GALLO, R C; GARTNER, S; LORI, F C; MARKHAM, P D; POPOVIC, M; REITZ, M S
PA (USSH) US DEPT HEALTH & HUMAN SERVICES
CYC 1
PI US 5869313 A 19990209 (199913)* 87p
ADT US 5869313 A Cont of US 1990-599491 19901017, Div ex US 1993-22835 19930225, Div ex US 1995-388809 19950215, US 1996-647714 19960514
FDT US 5869313 A Div ex US 5420030, Div ex US 5576000
PRAI US 1990-599491 19901017; US 1993-22835 19930225; US 1995-388809 19950215; US 1996-647714 19960514

L16 ANSWER 6 OF 10 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
Full Text
AN 1997-011206 [01] WPIDS
CR 1991-346752 [47]; 1999-152779 [13]
DNC C1997-002987
TI New isolated envelope protein of **HIV**-1 strain BA-L and recombinant equivalents - useful as immunogens for vaccines and antibody prodn., typical of US clinical isolates.
DC B04 D16
IN **FRANCHINI, G**; GALLO, R C; GARTNER, S; LORI, F C; MARKHAM, P D; POPOVIC, M; REITZ, M S
PA (USSH) US DEPT HEALTH & HUMAN SERVICES
CYC 1
PI US 5576000 A 19961119 (199701)* 86p
ADT US 5576000 A Cont of US 1990-599491 19901017, Div ex US 1993-22835 19930225, US 1995-388809 19950215
FDT US 5576000 A Div ex US 5420030
PRAI US 1990-599491 19901017; US 1993-22835 19930225; US 1995-388809 19950215

L16 ANSWER 7 OF 10 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
Full Text
AN 1995-366231 [47] WPIDS
CR 1983-707055 [28]; 1988-056484 [08]; 1989-130047 [17]; 1990-305017 [40]; 1990-348485 [46]; 1992-096889 [12]; 1992-175125 [21]; 1992-200174 [24]; 1992-268664 [32]; 1992-331718 [40]; 1992-349203 [42]; 1993-018128 [02]; 1993-026900 [03]; 1993-076502 [09]; 1993-243234 [30]; 1994-263767 [32]; 1995-036113 [05]; 1995-366385 [47]; 1996-187644 [19]; 1997-042857 [04]; 1997-043114 [04]; 1997-051904 [05]; 1998-321465 [28]; 1998-332054 [29]; 1998-332055 [29]; 1998-332145 [29]; 1999-493494 [41]; 1999-610231 [52]; 2001-280989 [29]; 2002-040232 [05]; 2003-567445 [53]
DNC C1995-159386
TI Virulence-attenuated virus encoding an immunodeficiency virus epitope - based on Copenhagen strain of vaccinia virus, used in the prevention and treatment of diseases, e.g. vaccination against **HIV**.
DC B04 D16
IN COX, W I; PAOLETTI, E; TARTAGLIA, J; **FRANCHINI, G**; GALLO, R
PA (VIRO-N) VIROGENETICS CORP; (COXW-I) COX W I; (FRAN-I) FRANCHINI G; (GALL-I) GALLO R; (PAOL-I) PAOLETTI E; (TART-I) TARTAGLIA J
CYC 21
PI WO 9527507 A1 19951019 (199547)* EN 208p
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE
W: AU CA JP
AU 9522755 A 19951030 (199606)

EP 752887 A1 19970115 (199708) EN

R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE

JP 09511649 W 19971125 (199806) 308p

EP 752887 A4 19970820 (199814)

US 5863542 A 19990126 (199911)

AU 702634 B 19990225 (199920)

AU 9931252 A 19990916 (199950)#

AU 747139 B 20020509 (200238)#

US 6596279 B1 20030722 (200354)

US 2003223987 A1 20031204 (200380)

ADT WO 9527507 A1 WO 1995-US3989 19950406; AU 9522755 A AU 1995-22755 19950406; EP 752887 A1 EP 1995-916151 19950406, WO 1995-US3989 19950406; JP 09511649 W JP 1995-526378 19950406, WO 1995-US3989 19950406; EP 752887 A4 EP 1995-916151 19950406; US 5863542 A CIP of US 1991-666056 19910307, CIP of US 1991-713967 19910611, CIP of US 1991-715921 19910614, Cont of US 1992-847951 19920306, CIP of US 1992-897382 19920611, CIP of US 1993-105483 19930813, CIP of US 1994-223842 19940406, US 1995-417210 19950405; AU 702634 B AU 1995-22755 19950406; AU 9931252 A Div ex AU 1995-22755 19950406, AU 1999-31252 19990525; AU 747139 B Div ex AU 1995-22755 19950406, AU 1999-31252 19990525; US 6596279 B1 CIP of US 1991-666056 19910307, CIP of US 1991-713967 19910611, CIP of US 1991-715921 19910614, Cont of US 1992-847951 19920306, CIP of US 1992-897382 19920611, CIP of US 1993-105483 19930812, CIP of US 1994-223842 19940406, Div ex US 1995-417210 19950405, US 1998-136159 19980814; US 2003223987 A1 CIP of US 1991-666056 19910307, CIP of US 1991-713967 19910611, CIP of US 1991-715921 19910614, CIP of US 1992-847951 19920306, CIP of US 1992-897382 19920611, CIP of US 1993-105483 19930812, CIP of US 1994-223842 19940406, Div ex US 1995-417210 19950405, Div ex US 1998-136159 19980814, US 2003-441788 20030520

FDT AU 9522755 A Based on WO 9527507; EP 752887 A1 Based on WO 9527507; JP 09511649 W Based on WO 9527507; US 5863542 A CIP of US 5494807; AU 702634 B Div ex AU 672359, Div ex AU 672581, Previous Publ. AU 9522755, Based on WO 9527507; AU 9931252 A Div ex AU 702634; AU 747139 B Div ex AU 702634, Previous Publ. AU 9931252; US 6596279 B1 CIP of US 5494807, Div ex US 5863542; US 2003223987 A1 CIP of US 5494807, Div ex US 5863542, Div ex US 6596279

PRAI US 1995-417210 19950405; US 1994-223842 19940406; US 1991-666056 19910307; US 1991-713967 19910611; US 1991-715921 19910614; US 1992-847951 19920306; US 1992-897382 19920611; US 1993-105483 19930813; AU 1999-31252 19990525; US 1998-136159 19980814; US 2003-441788 20030520

L16 ANSWER 8 OF 10 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN

Full Text

AN 1993-018128 [02] WPIDS

CR 1983-707055 [28]; 1988-056484 [08]; 1989-130047 [17]; 1990-305017 [40]; 1990-348485 [46]; 1992-096889 [12]; 1992-175125 [21]; 1992-200174 [24]; 1992-268664 [32]; 1992-331718 [40]; 1992-349203 [42]; 1993-026900 [03]; 1993-076502 [09]; 1993-243234 [30]; 1994-263767 [32]; 1995-036113 [05]; 1995-366231 [47]; 1995-366385 [47]; 1996-187644 [19]; 1997-042857 [04]; 1997-043114 [04]; 1997-051904 [05]; 1998-321465 [28]; 1998-332054 [29]; 1998-332055 [29]; 1998-332145 [29]; 1999-493494 [41]; 1999-610231 [52]; 2001-280989 [29]; 2002-040232 [05]; 2003-567445 [53]

DNC C1993-008315

TI Modified recombinant virus with inactivated non-essential genetic functions - comprises e.g. vaccinia or avipox virus, used as **HIV** vaccine.

DC B04 C06 D16

IN COX, W I; PAOLETTI, E; TARTAGLIA, J; **FRANCHINI, G**; GALLO, R

PA (VIRO-N) VIROGENETICS CORP; (USSH) US DEPT HEALTH & HUMAN SERVICES

CYC 20

PI WO 9222641 A1 19921223 (199302)* EN 159p

RW: AT BE CH DE DK ES FR GB GR IT LU MC NL SE

W: AU CA JP KR

AU 9222597 A 19930112 (199317)

EP 592546 A1 19940420 (199416) EN

R: AT BE CH DE DK ES FR GB GR IT LI LU MC NL SE
JP 06508037 W 19940914 (199441)
EP 592546 A4 19941012 (199534)
AU 672581 B 19961010 (199648)
AU 9665645 A 19970213 (199715)
AU 9665646 A 19970213 (199715)
US 5766598 A 19980616 (199831)
AU 712431 B 19991104 (200003)
AU 716480 B 20000224 (200020)
EP 1156102 A1 20011121 (200176) EN
R: AT BE CH DE DK ES FR GB GR IT LI LU MC NL SE
EP 592546 B1 20030528 (200336) EN
R: AT BE CH DE DK ES FR GB GR IT LI LU MC NL SE
DE 69233080 E 20030703 (200351)
JP 3504659 B2 20040308 (200418) 77p

ADT WO 9222641 A1 WO 1992-US5107 19920612; AU 9222597 A AU 1992-22597 19920612; EP 592546 A1 EP 1992-914713 19920612, WO 1992-US5107 19920612; JP 06508037 W WO 1992-US5107 19920612, JP 1993-501091 19920612; EP 592546 A4 EP 1992-914713 ; AU 672581 B Div ex AU 1992-15871 19920309, AU 1992-22597 19920612; AU 9665645 A Div ex AU 1992-22597 19920612, AU 1996-65645 19960916; AU 9665646 A Div ex AU 1992-22597 19920612, AU 1996-65646 19960916; US 5766598 A CIP of US 1991-666056 19910307, CIP of US 1991-713967 19910611, CIP of US 1991-715921 19910614, CIP of US 1992-847951 19920306, Cont of US 1992-897382 19920611, US 1994-303275 19940907; AU 712431 B AU 1996-65646 19960916; AU 716480 B AU 1996-65645 19960916; EP 1156102 A1 Div ex EP 1992-914713 19920612, EP 2001-111929 19920612; EP 592546 B1 EP 1992-914713 19920612, WO 1992-US5107 19920612; DE 69233080 E DE 1992-633080 19920612, EP 1992-914713 19920612, WO 1992-US5107 19920612; JP 3504659 B2 WO 1992-US5107 19920612, JP 1993-501091 19920612

FDT AU 9222597 A Based on WO 9222641; EP 592546 A1 Based on WO 9222641; JP 06508037 W Based on WO 9222641; AU 672581 B Previous Publ. AU 9222597, Based on WO 9222641; AU 712431 B Div ex AU 672359, Previous Publ. AU 9665646; AU 716480 B Div ex AU 672359, Previous Publ. AU 9665645; EP 1156102 A1 Div ex EP 592546; EP 592546 B1 Based on WO 9222641; DE 69233080 E Based on EP 592546, Based on WO 9222641; JP 3504659 B2 Previous Publ. JP 06508037, Based on WO 9222641

PRAI US 1992-897382 19920611; US 1991-715921 19910614; US 1991-666056 19910307; US 1991-713967 19910611; US 1992-847951 19920306; US 1994-303275 19940907

L16 ANSWER 9 OF 10 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
Full Text
AN 1991-346752 [47] WPIDS
CR 1997-011206 [01]; 1999-152779 [13]
DNC C1991-149464
TI US **HIV**-1 isolates MN-ST1 and BA-L, ENV protein and DNA - are useful in therapeutics, vaccines and diagnostic tests.
DC B04 D16
IN **FRANCHINI, G**; GALLO, R C; GARNTER, S; LON, F C; MARKHAM, P D; POPOVIC, M; REITZ, M S; LORI, F C; GARNTER, S N; REITZ, M; GARTNER, S
PA (USDC) US DEPT OF COMMERCE; (USSH) NAT INST OF HEALTH; (USGO) US GOVERNMENT; (USSH) US DEPT HEALTH & HUMAN SERVICES; (USDC) US SEC OF COMMERCE
CYC 18
PI US 599491 A0 19911015 (199147)* 61p
WO 9206990 A1 19920430 (199220) EN 55p
RW: AT BE CH DE DK ES FR GB GR IT LU NL SE
W: AU CA JP
AU 9189363 A 19920520 (199233)
EP 554389 A1 19930811 (199332) EN 55p
R: AT BE CH DE DK ES FR GB GR IT LI LU NL SE
JP 05507205 W 19931021 (199347) 55p
AU 649502 B 19940526 (199426)
US 5420030 A 19950530 (199527)
EP 554389 A4 19940706 (199532)

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EP 554389      B1 19980304 (199815)  EN     43p
        R: AT BE CH DE DK ES FR GB GR IT LI LU NL SE
     DE 69129034    E  19980409 (199820)
     JP 2767078     B2 19980618 (199829)        48p
     ES 2115622     T3 19980701 (199832)
     EP 554389      B2 20020814 (200255)  EN
        R: AT BE CH DE DK ES FR GB GR IT LI LU NL SE
ADT  US 599491 A0 US 1990-183830 19901017; WO 9206990 A1 WO 1991-US7611
     19911017; AU 9189363 A AU 1991-89363 19911017, WO 1991-US7611 19911017; EP
     554389 A1 EP 1991-920794 19911017, WO 1991-US7611 19911017; JP 05507205 W
     JP 1991-518591 19911017, WO 1991-US7611 19911017; AU 649502 B AU
     1991-89363 19911017; US 5420030 A Cont of US 1990-599491 19901017, US
     1993-22835 19930225; EP 554389 A4 EP 1991-920794         ; EP 554389 B1 EP
     1991-920794 19911017, WO 1991-US7611 19911017; DE 69129034 E DE
     1991-629034 19911017, EP 1991-920794 19911017, WO 1991-US7611 19911017; JP
     2767078 B2 JP 1991-518591 19911017, WO 1991-US7611 19911017; ES 2115622 T3
     EP 1991-920794 19911017; EP 554389 B2 EP 1991-920794 19911017, WO
     1991-US7611 19911017
FDT  AU 9189363 A Based on WO 9206990; EP 554389 A1 Based on WO 9206990; JP
     05507205 W Based on WO 9206990; AU 649502 B Previous Publ. AU 9189363,
     Based on WO 9206990; EP 554389 B1 Based on WO 9206990; DE 69129034 E Based
     on EP 554389, Based on WO 9206990; JP 2767078 B2 Previous Publ. JP
     05507205, Based on WO 9206990; ES 2115622 T3 Based on EP 554389; EP 554389
     B2 Based on WO 9206990
PRAI US 1990-183830   19901017; US 1990-599491   19901017; US 1993-22835
     19930225

L16  ANSWER 10 OF 10  WPIDS  COPYRIGHT 2004 THOMSON DERWENT on STN
Full Text
AN   1989-339698 [46]   WPIDS
DNC  C1989-150543
TI   Complete human immuno-deficiency type 2 pro-viral clone - used to generate
     animal model for function studies of HIV genes in vivo.
DC   B04 D16
IN   FRANCHINI, G; GALLO, R; WONG-STAAL, F; WONGSTAAL, F
PA   (USDC) US DEPT OF COMMERCE; (USSH) US DEPT HEALTH & HUMAN SERVICE; (USDC)
     US SEC OF COMMERCE; (USGO) US GOVERNMENT
CYC  17
PI   US 331212      A0 19890829 (198946)*
     WO 9012021     A  19901018 (199044)
       RW: AT BE CH DE DK ES FR GB IT LU NL SE
        W: AU CA JP LU
     AU 9053536     A  19901105 (199105)
     EP 478556      A  19920408 (199215)        78p
        R: AT BE CH DE DK ES FR GB IT LI LU NL SE
     JP 04504358    W  19920806 (199238)        29p
     US 5223423     A  19930629 (199327)        36p
     AU 648983      B  19940512 (199425)
     EP 478556      A4 19920902 (199523)
ADT  EP 478556 A EP 1990-905797 19900322; JP 04504358 W JP 1990-505498
     19900322, WO 1990-US1446 19900322; US 5223423 A US 1989-331212 19890331;
     AU 648983 B AU 1990-53536 19900322; EP 478556 A4 EP 1990-905797
FDT  EP 478556 A Based on WO 9012021; JP 04504358 W Based on WO 9012021; AU
     648983 B Previous Publ. AU 9053536, Based on WO 9012021
PRAI US 1989-331212   19890331


=> e shearer g m/in
E1           1      SHEARER F W/IN
E2           6      SHEARER G/IN
E3          10 --> SHEARER G M/IN
E4           1      SHEARER G N/IN
E5           5      SHEARER G W/IN
E6           1      SHEARER H A/IN
E7           3      SHEARER H D/IN
E8           1      SHEARER I J/IN
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E9             1      SHEARER J/IN
E10            7      SHEARER J A/IN
E11            3      SHEARER J B/IN
E12            3      SHEARER J D/IN

=> s e3
L17          10 "SHEARER G M"/IN

=> s e3 or e2
             10 "SHEARER G M"/IN
              6 "SHEARER G"/IN
L18          15 "SHEARER G M"/IN OR "SHEARER G"/IN

=> d l18,bib,1-15

L18  ANSWER 1 OF 15  WPIDS  COPYRIGHT 2004 THOMSON DERWENT on STN
Full Text
AN   2003-504994 [47]   WPIDS
DNC  C2003-134858
TI   Thermoplastic elastomer composition for use in fabricating e.g. wire and
     cable insulation comprises silicone elastomer and thermoplastic
     polyurethane elastomer.
DC   A25 E19
IN   GORNOWICZ, G A; GROSS, C S; HARTMANN, M D; LIAO, J; SAGE, J P; SHEARER, G
     N; TANGNEY, T J; GORNOWICZ, G; GROSS, C; HARTMANN, M; SAGE, J; SHEARER,
     G; TANGNEY, T
PA   (GORN-I) GORNOWICZ G A; (GROS-I) GROSS C S; (HART-I) HARTMANN M D;
     (LIAO-I) LIAO J; (SAGE-I) SAGE J P; (SHEA-I) SHEARER G N; (TANG-I) TANGNEY
     T J; (DOWO) DOW CORNING CORP
CYC  101
PI   WO 2003035757 A1 20030501 (200347)* EN   33p
        RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU
            MC MW MZ NL OA PT SD SE SK SL SZ TR TZ UG ZM ZW
         W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK
            DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR
            KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT
            RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA
            ZM ZW
     US 2003109623 A1 20030612 (200347)
ADT  WO 2003035757 A1 WO 2002-US33901 20021022; US 2003109623 A1 Provisional US
     2001-347785P 20011023, Provisional US 2002-411253P 20020916, US
     2002-278532 20021023
PRAI US 2002-411253P  20020916; US 2001-347785P  20011023; US 2002-278532
     20021023

L18  ANSWER 2 OF 15  WPIDS  COPYRIGHT 2004 THOMSON DERWENT on STN
Full Text
AN   2002-048836 [06]   WPIDS
DNC  C2002-013601
TI   Vaccinating against a human immunodeficiency virus/mammalian retrovirus
     comprises selecting an immunogen and administering the immunogen.
DC   B04
IN   BENVENISTE, R E; CLERICI, M S; SHEARER, G M
PA   (USSH) US DEPT HEALTH & HUMAN SERVICES
CYC  1
PI   US 2001043932 A1 20011122 (200206)*       12p
ADT  US 2001043932 A1 Cont of US 1994-250417 19940527, Cont of US 1997-899081
     19970723, Cont of US 1999-321498 19990527, US 2001-769223 20010124
PRAI US 1994-250417   19940527; US 1997-899081   19970723; US 1999-321498
     19990527; US 2001-769223   20010124

L18  ANSWER 3 OF 15  WPIDS  COPYRIGHT 2004 THOMSON DERWENT on STN
Full Text
AN   2001-343019 [36]   WPIDS
DNC  C2001-106103
TI   Stimulating CD8(+) response in retrovirus-infected human, involves
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administering nucleic acid based vaccine to produce retrovirus specific
peptides for cell MHC class I molecules.
DC B04 D16
IN FRANCHINI, G; HEL, Z; NACSA, J; **SHEARER, G**; TARTAGLIA, J
PA (USSH) US DEPT HEALTH & HUMAN SERVICES
CYC 95
PI WO 2001008702 A2 20010208 (200136)* EN 37p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ
NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM
DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC
LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE
SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2000066128 A 20010219 (200136)
EP 1198248 A2 20020424 (200235) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT
RO SE SI
JP 2003505516 W 20030212 (200321) 59p
ADT WO 2001008702 A2 WO 2000-US20641 20000727; AU 2000066128 A AU 2000-66128
20000727; EP 1198248 A2 EP 2000-953728 20000727, WO 2000-US20641 20000727;
JP 2003505516 W WO 2000-US20641 20000727, JP 2001-513432 20000727
FDT AU 2000066128 A Based on WO 2001008702; EP 1198248 A2 Based on WO
2001008702; JP 2003505516 W Based on WO 2001008702
PRAI US 2000-200445P 20000428; US 1999-146240P 19990728; US 2000-178989P
20000128

L18 ANSWER 4 OF 15 WPIDS
Full Text
AN 2001-032291 [04] WPIDS
DNC C2001-009947
TI Composition for treating viral infections, e.g. human immunodeficiency
virus, and cancer e.g. B cell lymphoma and leukemia, comprises a
semi-allogeneic hybrid fusion cell and an immunogenic peptide.
DC B04 D16
IN BERZOFSKY, J A; BROWN, E A; DEGROOT, A S; GATTONI-CELLI, S; GRENE, E;
NEWTON, D A; **SHEARER, G**
PA (UYSC-N) UNIV SOUTH CAROLINA; (USSH) US DEPT HEALTH & HUMAN SERVICES
CYC 92
PI WO 2000076537 A2 20001221 (200104)* EN 95p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL
OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ
EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK
LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI
SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2000048016 A 20010102 (200121)
ADT WO 2000076537 A2 WO 2000-US11008 20000424; AU 2000048016 A AU 2000-48016
20000424
FDT AU 2000048016 A Based on WO 2000076537
PRAI US 1999-254556 19990616

L18 ANSWER 5 OF 15 WPIDS
Full Text
AN 2000-638236 [61] WPIDS
DNC C2000-191955
TI Inhibiting immune responses to selected antigens for treating immune
mediated diseases, by incubating antigen presenting cells with composition
comprising factors secreted by glioblastoma cell line.
DC B04 D16
IN CHOUGNET, C; COLIGAN, J E; **SHEARER, G M**; ZUO, J; ZOU, J
PA (USSH) US DEPT HEALTH & HUMAN SERVICES; (USSH) US NAT INST OF HEALTH
CYC 93
PI WO 2000056356 A2 20000928 (200061)* EN 63p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL
OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ

EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK
LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI
SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2000040295 A 20001009 (200103)
EP 1165101 A2 20020102 (200209) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT
RO SE SI
JP 2002539271 W 20021119 (200281) 69p
ADT WO 2000056356 A2 WO 2000-US7959 20000323; AU 2000040295 A AU 2000-40295
20000323; EP 1165101 A2 EP 2000-919639 20000323, WO 2000-US7959 20000323;
JP 2002539271 W JP 2000-606260 20000323, WO 2000-US7959 20000323
FDT AU 2000040295 A Based on WO 2000056356; EP 1165101 A2 Based on WO
2000056356; JP 2002539271 W Based on WO 2000056356
PRAI US 1999-125996P 19990324

L18 ANSWER 6 OF 15 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
Full Text
AN 2000-271254 [23] WPIDS
DNC C2000-082764
TI Treating Kaposi's sarcoma and inhibiting angiogensis in a lesion
associated with Kaposi's sarcoma, comprising administering interleukin-12
(IL-12).
DC B04
IN FIEGAL, E; LIETZAU, J; LITTLE, R; PLUDA, J M; **SHEARER, G M**; SHERMAN, M
L; TOSATO, G; WYVILL, K; YARCHOAN, R; FEIGAL, E
PA (GEMY) GENETICS INST LLC; (USSH) US DEPT HEALTH & HUMAN SERVICES; (GEMY)
GENETICS INST INC; (USSH) US NAT INST OF HEALTH; (AMHP) WYETH
CYC 84
PI WO 2000015249 A1 20000323 (200023)* EN 56p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL
OA PT SD SE SL SZ TZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE
GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG
MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG
UZ VN YU ZW
AU 9962490 A 20000403 (200034)
EP 1030680 A1 20000830 (200042) EN
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
US 6423308 B1 20020723 (200254)
JP 2002524530 W 20020806 (200266) 50p
US 6509321 B1 20030121 (200309)
AU 761520 B 20030605 (200341)
US 2003190305 A1 20031009 (200367)#
AU 2003231607 A1 20030911 (200422)#
ADT WO 2000015249 A1 WO 1999-US21199 19990915; AU 9962490 A AU 1999-62490
19990915; EP 1030680 A1 EP 1999-949660 19990915, WO 1999-US21199 19990915;
US 6423308 B1 Provisional US 1998-100416P 19980915, US 1999-396931
19990915; JP 2002524530 W WO 1999-US21199 19990915, JP 2000-569833
19990915; US 6509321 B1 Provisional US 1998-100416P 19980915, Div ex US
1999-396931 19990915, US 2000-672448 20000929; AU 761520 B AU 1999-62490
19990915; US 2003190305 A1 Div ex US 1999-396931 19990915, Div ex US
2000-672448 20000929, US 2002-307295 20021202; AU 2003231607 A1 Div ex AU
1999-62490 19990915, AU 2003-231607 20030801
FDT AU 9962490 A Based on WO 2000015249; EP 1030680 A1 Based on WO 2000015249;
JP 2002524530 W Based on WO 2000015249; AU 761520 B Previous Publ. AU
9962490, Based on WO 2000015249; US 2003190305 A1 Div ex US 6423308, Div
ex US 6509321
PRAI US 1998-100416P 19980915; US 1999-396931 19990915; US 2000-672448
20000929; US 2002-307295 20021202; AU 2003-231607 20030801

L18 ANSWER 7 OF 15 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
Full Text
AN 1997-108658 [10] WPIDS
DNN N1997-089944 DNC C1997-034620
TI Diagnosis of exposure to infectious agents, partic. HIV - by detecting
activation of peripheral blood mononuclear cells from patient by epitope

of infectious agent.
DC B04 D16 S03
IN BERZOFSKY, J A; CLERICI, M; **SHEARER, G M**
PA (USSH) US SEC DEPT HEALTH; (USSH) US DEPT HEALTH & HUMAN SERVICES
CYC 70
PI WO 9641189 A1 19961219 (199710)* EN 82p
RW: AT BE CH DE DK EA ES FI FR GB GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG
W: AL AM AT AU AZ BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE HU IS JP KE KG KP KR KZ LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG US UZ VN
AU 9661118 A 19961230 (199716)
ADT WO 9641189 A1 WO 1996-US10108 19960607; AU 9661118 A AU 1996-61118 19960607
FDT AU 9661118 A Based on WO 9641189
PRAI US 1995-488435 19950607

L18 ANSWER 8 OF 15 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
Full Text
AN 1996-117413 [13] WPIDS
DNC C1996-037266
TI Vaccination of humans against HIV - by admin. of an immunogen which induces a sustained cell-mediated immune response against HIV but does not activate a humoral response.
DC B04 D16
IN BENVENISTE, R E; CLERICI, M S; **SHEARER, G M**
PA (USSH) US DEPT HEALTH & HUMAN SERVICES
CYC 1
PI CA 2124545 A 19951128 (199613)* EN 33p
ADT CA 2124545 A CA 1994-2124545 19940527
PRAI CA 1994-2124545 19940527

L18 ANSWER 9 OF 15 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
Full Text
AN 1994-317036 [39] WPIDS
DNN N1994-248871 DNC C1994-144529
TI Use of calpain inhibitors - to inhibit or reverse calpain-mediated programmed cell death in immunodeficiency diseases, by HIV infection.
DC B04 D16 S03
IN CLERICI, M; HENKART, P; SARIN, A; **SHEARER, G M**
PA (USSH) US SEC DEPT HEALTH; (USSH) US DEPT HEALTH & HUMAN SERVICES
CYC 2
PI WO 9421817 A1 19940929 (199439)* EN 40p
AU 9463674 A 19941011 (199504)
US 5607831 A 19970304 (199715) 18p
ADT WO 9421817 A1 WO 1994-US2946 19940318; AU 9463674 A AU 1994-63674 19940318; US 5607831 A US 1993-37578 19930325
FDT AU 9463674 A Based on WO 9421817
PRAI US 1993-37578 19930325

L18 ANSWER 10 OF 15 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
Full Text
AN 1994-118169 [14] WPIDS
DNC C1994-054658
TI Increasing interleukin-2 prodn. in T helper cells - of HIV patients, by admin. of interleukin 10 antagonist, pref. antibody..
DC B04
IN CLERICI, M; COFFMAN, R L; **SHEARER, G M**
PA (SCHE) SCHERING CORP; (USSH) US DEPT HEALTH & HUMAN SERVICES; (USSH) US SEC DEPT HEALTH
CYC 2
PI WO 9406473 A1 19940331 (199414)* EN 11p
AU 9348567 A 19940412 (199431)
EP 667789 A1 19950823 (199538) EN
JP 08501549 W 19960220 (199643) 10p
ADT WO 9406473 A1 WO 1993-US8562 19930916; AU 9348567 A AU 1993-48567

19930916, EP 667789 A1 EP 1993-921492 19930916, WO 1993-US8562 19930916,
JP 08501549 W WO 1993-US8562 19930916, JP 1994-508193 19930916
FDT AU 9348567 A Based on WO 9406473; EP 667789 A1 Based on WO 9406473; JP
08501549 W Based on WO 9406473
PRAI US 1992-947316 19920918

L18 ANSWER 11 OF 15 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
Full Text
AN 1992-007208 [01] WPIDS
CR 1989-300689 [41]
DNC C1992-003082
TI Detection of immune dysfunction - by comparing IL-2 prodn. by peripheral
blood leukocytes from patients in response to recall antigens.
DC B04
IN CLERICI, M; GRESS, R E; LUCAS, P J; **SHEARER, G M**; VIA, C S; LUCAS, P;
VIA, C; LUCUS, P J
PA (USDC) US DEPT OF COMMERCE; (USDC) US SEC OF COMMERCE; (USSH) US DEPT
HEALTH & HUMAN SERVICES; (USSH) US DEPT HEALTH & HUMAN SERVICE
CYC 18
PI WO 9118626 A 19911212 (199201)*
RW: AT BE CH DE DK ES FR GB GR IT LU NL SE
W: AU CA JP
AU 9181865 A 19911231 (199215)
US 535407 A0 19921201 (199301) 47p
JP 05506720 W 19930930 (199344)
EP 593471 A1 19940427 (199417) EN
R: AT BE CH DE DK ES FR GB GR IT LI LU NL SE
US 5344755 A 19940906 (199435) 19p
AU 654668 B 19941117 (199502)
US 5514556 A 19960507 (199624) 19p
JP 2969197 B2 19991102 (199951) 23p
CA 2084883 C 20001226 (200104) EN
ADT US 535407 A0 US 1990-535407 19900608; JP 05506720 W JP 1991-511761
19910610, WO 1991-US4010 19910610; EP 593471 A1 EP 1991-912615 19910610,
WO 1991-US4010 19910610; US 5344755 A CIP of US 1989-341360 19890421, US
1990-535407 19900608; AU 654668 B AU 1991-81865 19910610; US 5514556 A CIP
of US 1989-341360 19890421, Div ex US 1990-535407 19900608, US 1994-185423
19940119; JP 2969197 B2 JP 1991-511761 19910610, WO 1991-US4010 19910610;
CA 2084883 C CA 1991-2084883 19910610, WO 1991-US4010 19910610
FDT JP 05506720 W Based on WO 9118626; EP 593471 A1 Based on WO 9118626; AU
654668 B Previous Publ. AU 9181865, Based on WO 9118626; US 5514556 A Div
ex US 5344755; JP 2969197 B2 Previous Publ. JP 05506720, Based on WO
9118626; CA 2084883 C Based on WO 9118626
PRAI US 1990-535407 19900608; US 1989-341360 19890421; US 1994-185423
19940119

L18 ANSWER 12 OF 15 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
Full Text
AN 1991-237706 [32] WPIDS
DNC C1991-103347
TI Peptide(s) contg. conserved epitope of HIV-1 reverse transcriptase - are
new and include cytotoxic T cells, useful in HIV vaccines effective
against different strains.
DC B04 D16
IN BERZOFSKY, J A; CLERICI, M; GERMAIN, R N; HOSMALIN, A; MOSS, B; PENDLETON,
C D; SCHEARER, G M; GERMAIN, R; **SHEARER, G**; **SHEARER, G M**; CLERICI, M S
PA (USDC) US DEPT OF COMMERCE; (USSH) US NAT CANCER INST; (USDC) US SEC OF
COMMERCE; (USSH) US DEPT HEALTH & HUMAN SERVICES
CYC 18
PI US 489825 A0 19910702 (199132)*
WO 9113910 A 19910919 (199140)
RW: AT BE CH DE DK ES FR GB GR IT LU NL SE
W: AU CA JP
AU 9175566 A 19911010 (199201)
EP 519013 A1 19921223 (199252) EN 31p
R: AT BE CH DE DK ES FR GB GR IT LI LU NL SE

AU 632683 B 19930107 (199308)
JP 05506647 W 19930930 (199344) 12p
US 5336758 A 19940809 (199431) 11p
EP 519013 A4 19930505 (199526)
JP 07110877 B2 19951129 (199601) 10p
CA 2077651 C 19970603 (199734)
ADT US 489825 A0 US 1991-489825 19910702; EP 519013 A1 EP 1991-907318 19910308, WO 1991-US1486 19910308; AU 632683 B AU 1991-75566 19910308; JP 05506647 W JP 1991-506562 19910308, WO 1991-US1486 19910308; US 5336758 A US 1990-489825 19900309; EP 519013 A4 EP 1991-907318 ; JP 07110877 B2 JP 1991-506562 19910308, WO 1991-US1486 19910308; CA 2077651 C CA 1991-2077651 19910308
FDT EP 519013 A1 Based on WO 9113910; AU 632683 B Previous Publ. AU 9175566, Based on WO 9113910; JP 05506647 W Based on WO 9113910; JP 07110877 B2 Based on JP 05506647, Based on WO 9113910
PRAI US 1991-489825 19910702; US 1990-489825 19900309

L18 ANSWER 13 OF 15 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
Full Text
AN 1989-300689 [41] WPIDS
CR 1992-007208 [01]
DNN N1989-229382 DNC C1989-132972
TI Detecting immune dysfunction - by comparing IL-2 prodn. by human peripheral blood leukocytes in response to recall antigens.
DC B04 D16 S03
IN **SHEARER, G M**
PA (USSH) US DEPT HEALTH & HUMAN SERVICE
CYC 1
PI US 341360 A0 19890725 (198941)* 40p
ADT US 341360 A0 US 1989-341360 19890421
PRAI US 1989-341360 19890421

L18 ANSWER 14 OF 15 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
Full Text
AN 1989-061325 [08] WPIDS
DNN N1989-046687
TI Variable frequency system for servo system - has nonlinear voltage controlled oscillator in linear combination with integrator and charge pump.
DC U13 U22 U23
IN LOFGREN, K M; OUYANG, K W; **SHEARER, G**
PA (WDIG-N) WESTERN DIGITAL CORP
CYC 27
PI WO 8901263 A 19890209 (198908)* EN 37p
RW: AT BE CH FR GB IT LU NL SE
W: AT AU BB BG BR CH DE DK FI GB HU JP KP KR LK LU MG MW NL NO RO SD SE US
AU 8823121 A 19890301 (198923)
US 4871979 A 19891003 (198949) 16p
US 5126692 A 19920630 (199229) 16p
ADT WO 8901263 A WO 1988-2624 19880801; US 4871979 A US 1987-80957 19870803; US 5126692 A Div ex US 1987-80957 19870803, US 1989-384279 19890721
FDT US 5126692 A Div ex US 4871979
PRAI US 1987-80957 19870803

L18 ANSWER 15 OF 15 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
Full Text
AN 1987-157267 [22] WPIDS
DNN N1987-117957
TI Voltage controlled oscillator for phase locked loop system - has automatic adjust circuitry monitoring input to voltage controlled oscillator in phase locked loop.
DC U23
IN FRANK, C; LOFGREN, K; **SHEARER, G**
PA (WDIG-N) WESTERN DIGITAL CORP
CYC 2

```
PI   US 4667170    A  19870519 (198722)         7p
     CA 1282128    C  19910326 (199117)
ADT  US 4667170 A US 1985-780553 19850926
PRAI US 1985-780553   19850926


=> e nacsa j/in
E1            1      NACOVEC F/IN
E2            1      NACRY P/IN
E3            3 --> NACSA J/IN
E4            1      NACSA L/IN
E5            1      NACSA Z/IN
E6            1      NACSEV N/IN
E7            7      NACSON S/IN
E8            1      NACSON Y/IN
E9            1      NACSU C/IN
E10           1      NACU G/IN
E11           2      NACU N/IN
E12           3      NACY C A/IN

=> s e3
L19           3 "NACSA J"/IN

=> d l19,bib,1-3

L19  ANSWER 1 OF 3  WPIDS  COPYRIGHT 2004 THOMSON DERWENT on STN
Full Text
AN   2001-376080 [40]   WPIDS
DNC  C2001-115170
TI   New 1,3-bis-(phenyl or benzyl)-1,3-bis-(substituted alkyl)-disiloxane
     derivatives, useful as cytostatic agents and for reversing multidrug
     resistance in malignant tumor cells.
DC   B03 B05
IN   GAAL, D; HEGYES, P; HEVER, A; KIESSIG, S; LAGE, H; MOLNAR, J; MUCSI, I;
     NACSA, J; SZABO, D; VARGA, A
PA   (VARG-I) VARGA A
CYC  22
PI   DE 19923801   C1 20010705 (200140)*        5p
     WO 2002040490 A1 20020523 (200240)# DE
        RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR
         W: HU JP US
ADT  DE 19923801 C1 DE 1999-19923801 19990519; WO 2002040490 A1 WO 2000-DE4110
     20001115
PRAI DE 1999-19923801 19990519; WO 2000-DE4110   20001115

L19  ANSWER 2 OF 3  WPIDS  COPYRIGHT 2004 THOMSON DERWENT on STN
Full Text
AN   2001-343019 [36]   WPIDS
DNC  C2001-106103
TI   Stimulating CD8(+) response in retrovirus-infected human, involves
     administering nucleic acid-based vaccine to produce retrovirus specific
     peptides for cell MHC class I molecules.
DC   B04 D16
IN   FRANCHINI, G; HEL, Z; NACSA, J; SHEARER, G; TARTAGLIA, J
PA   (USSH) US DEPT HEALTH & HUMAN SERVICES
CYC  95
PI   WO 2001008702 A2 20010208 (200136)* EN   37p
        RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ
            NL OA PT SD SE SL SZ TZ UG ZW
         W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM
            DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC
            LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE
            SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
     AU 2000066128 A  20010219 (200136)
     EP 1198248    A2 20020424 (200235)  EN
         R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT
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RO SE SI
JP 2003505516 W 20030212 (200321) 59p
ADT WO 2001008702 A2 WO 2000-US20641 20000727; AU 2000066128 A AU 2000-66128 20000727; EP 1198248 A2 EP 2000-953728 20000727, WO 2000-US20641 20000727; JP 2003505516 W WO 2000-US20641 20000727, JP 2001-513432 20000727
FDT AU 2000066128 A Based on WO 2001008702; EP 1198248 A2 Based on WO 2001008702; JP 2003505516 W Based on WO 2001008702
PRAI US 2000-200445P 20000428; US 1999-146240P 19990728; US 2000-178989P 20000128

L19 ANSWER 3 OF 3 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
Full Text
AN 1986-313709 [48] WPIDS
DNC C1986-135593
TI Insulating building panels - made by mixing fibrous vegetable waste with water contg. synthetic resin bond improving agent, adding silicate based binder and water.
DC A93 L02 P64 Q44
IN HORVATH, I; JUHASZ, K; **NACSA, J**; POLHAMMER, E
PA (TWEN-N) 23 SZAMU ALLAMI EPI; (SZAM-N) SZAMU ALLAMI EQITOI; (TWOT-N) 23 SZAMU ALLAMI EPITOIPARI VALLALAT
CYC 9

PI	GB 2175294	A	19861126	(198648)*	6p
	NL 8501539	A	19861216	(198702)	
	AU 8542780	A	19861127	(198703)	
	DE 3517778	A	19870115	(198703)	
	JP 61295267	A	19861226	(198706)	
	BR 8502727	A	19870113	(198708)	
	CN 85104573	A	19861210	(198748)	
	IT 1184593	B	19871028	(199041)#	
	KR 9309890	B1	19931013	(199437)#	

ADT GB 2175294 A GB 1985-12500 19850517; NL 8501539 A NL 1985-1539 19850530; DE 3517778 A DE 1985-3517778 19850517; JP 61295267 A JP 1985-120347 19850603; KR 9309890 B1 KR 1985-4190 19850614
PRAI GB 1985-12500 19850517

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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	147.84	185.09

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FILE LAST UPDATED: 1 Apr 2004 (20040401/ED)
HIGHEST GRANTED PATENT NUMBER: US6715148
HIGHEST APPLICATION PUBLICATION NUMBER: US2004064864
CA INDEXING IS CURRENT THROUGH 1 Apr 2004 (20040401/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 1 Apr 2004 (20040401/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Feb 2004
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Feb 2004

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>>> published document but also a list of any subsequent <<<
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>>> publication date for all the US publications for an invention <<<
>>> are displayed in the PI (Patent Information) field of USPATFULL <<<
>>> records and may be searched in standard search fields, e.g., /PN, <<<
>>> /PK, etc. <<<

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>>> classifications, or claims, that may potentially change from    <<<
>>> the earliest to the latest publication.                         <<<

This file contains CAS Registry Numbers for easy and accurate
substance identification.

=> s (HIV or human immunodeficiency virus)
         30123 HIV
        379475 HUMAN
         17429 IMMUNODEFICIENCY
         71770 VIRUS
         12468 HUMAN IMMUNODEFICIENCY VIRUS
                 (HUMAN(W)IMMUNODEFICIENCY(W)VIRUS)
L20      31746 (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)

=> s l20 and (CTL or cytotoxic)
          8138 CTL
         28973 CYTOTOXIC
L21      10927 L20 AND (CTL OR CYTOTOXIC)

=> s l21 and (HIV/clm or human immunodeficiency virus/clm)
          4475 HIV/CLM
         72739 HUMAN/CLM
          1886 IMMUNODEFICIENCY/CLM
         12254 VIRUS/CLM
          1399 HUMAN IMMUNODEFICIENCY VIRUS/CLM
                 ((HUMAN(W)IMMUNODEFICIENCY(W)VIRUS)/CLM)
L22       1761 L21 AND (HIV/CLM OR HUMAN IMMUNODEFICIENCY VIRUS/CLM)

=> s l22 and (CTL/clm or cytotoxic/clm)
           312 CTL/CLM
          2456 CYTOTOXIC/CLM
L23        233 L22 AND (CTL/CLM OR CYTOTOXIC/CLM)

=> s l23 and (vaccin? or immunogen?)
         35572 VACCIN?
         35708 IMMUNOGEN?
L24        186 L23 AND (VACCIN? OR IMMUNOGEN?)

=> s l24 and (protect? or prevent?)
        925200 PROTECT?
       1889012 PREVENT?
L25        182 L24 AND (PROTECT? OR PREVENT?)

=> s l25 and (DNA/clm or nucleic acid/clm)
         29510 DNA/CLM
         29837 NUCLEIC/CLM
        304393 ACID/CLM
         28006 NUCLEIC ACID/CLM
                 ((NUCLEIC(W)ACID)/CLM)
L26         96 L25 AND (DNA/CLM OR NUCLEIC ACID/CLM)

=> s l26 and ay<2000
       2990872 AY<2000
L27         33 L26 AND AY<2000

=> d l27,cbib,ab,1-33

L27  ANSWER 1 OF 33  USPATFULL on STN
2004:7101 REDIRECTION OF CELLULAR IMMUNITY BY RECEPTOR CHIMERAS.
    SEED, BRIAN, BOSTON, MA, UNITED STATES
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ROMEO, CHARLES, BELMONT, MA, UNITED STATES
KOLANUS, WALDEMAR, WATERTOWN, MA, UNITED STATES
US 2004005334 A1 20040108
APPLICATION: US 1999-243008 A1 19990202 (9) <--
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Disclosed is a method of directing a cellular response in a mammal by expressing in a cell of the mammal a chimeric receptor which causes the cells to specifically recognize and destroy an infective agent, a cell infected with an infective agent, a tumor or cancerous cell, or an autoimmune-generated cell. Also disclosed are cells which express the chimeric receptors and DNA encoding the chimeric receptors.

L27 ANSWER 2 OF 33 USPATFULL on STN
2003:314466 **HIV**-specific T-cell induction.
Sastry, K. Jagannadha, Bastrop, TX, United States
Arlinghaus, Ralph B., Bellaire, TX, United States
Nehete, Pramod N., Bastrop, TX, United States
Board of Regents, The University of Texas System, Austin, TX, United States (U.S. corporation)
US 6656471 B1 20031202
APPLICATION: US 1999-440772 19991116 (9) <--
PRIORITY: US 1998-108563P 19981116 (60)
US 1999-115175P 19990108 (60)
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention discloses diagnostic, **preventative**, and treatment therapies of AIDS involving determining whether a subject exhibits an HLA-Cw7-restricted **CTL** response. Some methods are directed to the use of HLA-Cw7 as a genetic marker for long-term non-progression and amenability to treatment therapies. Diagnostic methods include a method for predicting long term non-progression in an **HIV**-infected subject. **Preventative** and treatment methods encompass determining whether a subject exhibits or can exhibit an HLA-Cw7-restricted **CTL** response. They also encompass ways of eliciting such a response, if necessary. Furthermore, some of the methods involve administering one or more **HIV** polypeptides or peptides, or polynucleotides encoding them, as a treatment therapy to **prevent** the development of AIDS.

L27 ANSWER 3 OF 33 USPATFULL on STN
2003:279110 Retrovirus and viral vectors.
Lauermann, Vit, Baltimore, MD, United States
Rubicon Laboratory, Inc., Baltimore, MD, United States (U.S. corporation)
US 6635472 B1 20031021
APPLICATION: US 1998-134360 19980814 (9) <--
PRIORITY: US 1997-55864P 19970815 (60)
US 1998-91734P 19980706 (60)
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention relates to the fields of genetic engineering, virus replication and gene transfer. More specifically, this invention relates to polynucleotide construct, recombinant virus, transposon, and their vectors, wherein an ori derived from a DNA virus capable of replicating in vertebrate cells is inserted into the retrovirus, allowing the retrovirus following the reverse transcription to efficiently replicate as extrachromosomal or episomal DNA without the necessity of integration into the host cell chromosome. Additionally, this invention relates to polynucleotide construct, recombinant virus, transposon, and their vectors replicating episomally without aid of an ori and related elements. Also, this invention encompasses **preventive**, therapeutic, and diagnostic applications employing said constructs, viruses and vectors.

L27 ANSWER 4 OF 33 USPATFULL on STN
2003:196946 Immunodeficiency recombinant poxvirus.
Paoletti, Enzo, Delmar, NY, United States

Tartaglia, James, Schenectady, NY, United States
Cox, William I., East Greenbush, NY, United States
Gallo, Robert, Baltimore, MD, United States
Franchini, Genoveffa, Washington, DC, United States
Virogenetics Corporation, Troy, NY, United States (U.S. corporation)
US 6596279 B1 20030722
APPLICATION: US 1998-136159 19980814 (9) <--
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Attenuated recombinant viruses containing DNA encoding an immunodeficiency virus and/or **CTL** antigen, as well as methods and compositions employing the viruses, expression products therefrom, and antibodies generated from the viruses or expression products, are disclosed and claimed. The recombinant viruses can be NYVAC or ALVAC recombinant viruses. The DNA can code for at least one of: HIV1gag(+pro)(IIIB), gp120(MN)(+transmembrane), nef(BRU)**CTL**, pol(IIIB)**CTL**, ELDKWA or LDKW epitopes, preferably HIV1gag(+pro)(IIIB), gp120(MN) (+transmembrane), two (2) nef(BRU)**CTL** and three (3) pol(IIIB)**CTL** etpitopes; or two ELDKWA in gp120 V3 or another region or in gp160. The two (2) nef(BRU)**CTL** and three (3) pol(IIIB)**CTL** epitopes are preferably CTL1, CTL2, pol1, pol2 and pol3. The recombinant viruses and gene products therefrom and antibodies generated by the viruses and gene products have several **preventive**, therapeutic and diagnostic uses. DNA from the recombinant viruses are useful as probes or, for generating PCR primers or for immunization. Also disclosed and claimed are **HIV immunogens** and modified gp160 and gp120.

L27 ANSWER 5 OF 33 USPATFULL on STN
2003:129925 Use of immunopotentiating sequences for inducing immune response.
McMillan, Minnie, Bradbury, CA, United States
University of Southern California, Los Angeles, CA, United States (U.S. corporation)
US 6562800 B1 20030513
APPLICATION: US 1999-430470 19991029 (9) <--
PRIORITY: US 1998-106506P 19981030 (60)
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides an **immunogenic** composition comprising a DNA expression vector encoding both an immunopotentiating chemokine sequence as well as an **immunogenic** polypeptide sequence. **Immunogenic** polypeptide sequences are those of infectious agents or of cancerous cells. Also provided are methods of manufacturing various **immunogenic** compositions, and methods of using such compositions to treat cancer and infectious disease.

L27 ANSWER 6 OF 33 USPATFULL on STN
2003:74293 **Vaccines** comprising synthetic genes.
Shiver, John W., Doylestown, PA, United States
Davies, Mary Ellen, Norristown, PA, United States
Freed, Daniel C., King of Prussia, PA, United States
Liu, Margaret A., Rosemont, PA, United States
Perry, Helen C., Lansdale, PA, United States
Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)
US 6534312 B1 20030318
APPLICATION: US 1999-340798 19990628 (9) <--
PRIORITY: US 1996-20166P 19960621 (60)
US 1996-20165P 19960621 (60)
US 1996-12082P 19960222 (60)
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Synthetic polynucleotides comprising a DNA sequence encoding a peptide or protein are provided. The DNA sequence of the synthetic polynucleotides comprise codons optimized for expression in a nonhomologous host. The invention is exemplified by synthetic DNA molecules encoding **HIV** env as well as modifications of **HIV** env. The codons of the synthetic molecules include the projected host cell's

preferred codons. The synthetic molecules provide preferred forms of foreign genetic material. The synthetic molecules may be used as a polynucleotide **vaccine** which provides immunoprophylaxis against **HIV** infection through neutralizing antibody and cell-mediated immunity. This invention provides polynucleotides which, when directly introduced into a vertebrate in vivo, including mammals such as primates and humans, induces the expression of encoded proteins within the animal.

L27 ANSWER 7 OF 33 USPATFULL on STN
2002:322019 METHOD FOR INDUCING IMMUNITY TO VIRUSES.
KANEKO, YUTARO, TOKYO, JAPAN
KOZBOR, DANUTA, PHILADELPHIA, PA, UNITED STATES
US 2002182180 A1 20021205
APPLICATION: US 1998-87513 A1 19980529 (9) <--
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to methods for inducing cellular immunity against viruses which undergo mutation by introducing a mutant form of an envelope (env) glycoprotein of the virus with an altered or deleted immunodominant epitope. Also disclosed are **vaccines** and methods of producing the same.

L27 ANSWER 8 OF 33 USPATFULL on STN
2002:251744 CHIMERIC RECEPTOR GENES AND CELLS TRANSFORMED THEREWITH.
ESHHAR, ZELIG A., REHOVOT, ISRAEL
SCHINDLER, DANIEL, REHOVOT, ISRAEL
WAKS, TOVA, PETACH TIKVA, ISRAEL
GROSS, GIDEON, HEVEL KORAZIM, ISRAEL
ROSENBERG, STEVEN A., POTOMAC, MD, UNITED STATES
HWU, PATRICK, ROCKVILLE, MD, UNITED STATES
US 2002137697 A1 20020926
APPLICATION: US 1995-547263 A1 19951024 (8) <--
PRIORITY: IL 1992-101288 19920318
IL 1993-104570 19930131
WO 1993-US2506 19930318
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Chimeric receptor genes suitable for endowing lymphocytes with antibody-type specificity include a first gene segment encoding a single-chain Fv domain of a specific antibody and a second gene segment encoding all or part of the transmembrane and cytoplasmic domains, and optionally the extracellular domain, of an immune cell-triggering molecule. The chimeric receptor gene, when transfected to immune cells, expresses the antibody-recognition site and the immune cell-triggering moiety into one continuous chain. The transformed lymphocytes are useful in therapeutic treatment methods.

L27 ANSWER 9 OF 33 USPATFULL on STN
2002:192074 IMMUNIZATION OF INFANTS.
BOT, ADRIAN, SAN DIEGO, CA, UNITED STATES
BONA, CONSTANTIN, NEW YORK, NY, UNITED STATES
US 2002103145 A1 20020801
APPLICATION: US 1999-308511 A1 19990519 (9) <--
WO 1997-US21687 19971121 <--
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to methods and compositions which may be used to immunize infant mammals against a target antigen, wherein an **immunogenically** effective amount of a nucleic acid encoding a relevant epitope of a desired target antigen is administered to the infant. It is based, at least in part, on the discovery that such genetic immunization of infant mammals could give rise to effective cellular and humoral immune responses against target antigens.

L27 ANSWER 10 OF 33 USPATFULL on STN
2002:171615 IMMUNOTHERAPY USING **CYTOTOXIC** T LYMPHOCYTES (**CTL**).

STRAUSS, HANS JOSEF, LONDON, UNITED KINGDOM
US 2002090362 A1 20020711
APPLICATION: US 1998-101413 A1 19980807 (9) <--
WO 1997-GB118 19970117
PRIORITY: GB 1996-878 19960117
GB 1996-23471 19961112
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method of treating a patient with a disease wherein the patient contains diseased cells which cells contain, or are associated with, an abnormal molecule or an abnormally elevated amount of a molecule and which cells are capable of presenting at least part of said molecule on their surface by an HLA class I (or equivalent) molecule, the method comprising administering to the patient a therapeutically effective amount of **cytotoxic** T lymphocytes (**CTL**) which recognize at least part of said molecule when presented by an HLA class I (or equivalent) molecule on the surface of a cell characterized in that the **cytotoxic** T lymphocytes are not derived from the patient with a disease. Preferably, the **CTL** are derived from an individual which individual does not carry the HLA class I (or equivalent) molecule type which, in the patient, presents at least part of said abnormal molecule, or molecule abnormally elevated, contained in or associated with the disease cells of said patient.

L27 ANSWER 11 OF 33 USPATFULL on STN
2002:157619 NON-**IMMUNOGENIC** PRODRUGS AND SELECTABLE MARKERS FOR USE IN GENE THERAPY.
JOLLY, DOUGLAS J., LEUCADIA, CA, UNITED STATES
MOORE, MARGARET D., SAN DIEGO, CA, UNITED STATES
CHADA, SUNIL, VISTA, CA, UNITED STATES
US 2002082224 A1 20020627
APPLICATION: US 1998-6298 A1 19980113 (9) <--
PRIORITY: US 1997-35473P 19970114 (60)
US 1997-38339P 19970227 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention provides methods for delivering a gene delivery vehicle to a warm-blooded animal, comprising the step of administering to a warm-blooded animal a gene delivery vehicle which directs the expression of a non-**immunogenic** selectable marker. Within other aspects, methods are provided for delivering a gene delivery vehicle to a warm-blooded animal, comprising the step of administering to a warm-blooded animal a gene delivery vehicle which directs the expression of a non-**immunogenic** molecule which is capable of activating an otherwise inactive compound into an active compound.

L27 ANSWER 12 OF 33 USPATFULL on STN
2002:102297 Self-enhancing, pharmacologically controllable expression systems.
Mueller, Rolf, Marburg, GERMANY, FEDERAL REPUBLIC OF
Sedlacek, Hans-Harald, Marburg, GERMANY, FEDERAL REPUBLIC OF
Aventis Pharma Deutschland GmbH, Frankfurt, GERMANY, FEDERAL REPUBLIC OF (non-U.S. corporation)
US 6383785 B1 20020507
APPLICATION: US 1997-987348 19971209 (8) <--
PRIORITY: DE 1996-19651443 19961211
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention relates to a nucleic acid construct which constitutes a self-enhancing expression system and which comprises the following components:

at least one first structural gene that encodes an active compound;

at least one second structural gene that encodes a transcription factor protein; and

at least one activation sequence comprised of at least one sequence that binds the transcription factor protein and at least one promoter sequence;

wherein each activation sequence activates the expression of a structural gene and the expression of the transcription factor protein; and to the use of the nucleic acid construct for preparing a drug for treating diseases.

L27 ANSWER 13 OF 33 USPATFULL on STN
2002:95770 Nucleic acid construct for the cell cycle regulated expression of structural genes.
Muller, Rolf, Marburg, GERMANY, FEDERAL REPUBLIC OF
Liu, Ningshu, Marburg, GERMANY, FEDERAL REPUBLIC OF
Zwicker, Jork, Marburg, GERMANY, FEDERAL REPUBLIC OF
Sedlacek, Hans-Harald, Marburg, GERMANY, FEDERAL REPUBLIC OF
Aventis Pharma Deutschland GmbH, Frankfurt, GERMANY, FEDERAL REPUBLIC OF (non-U.S. corporation)
US 6380170 B1 20020430
APPLICATION: US 1998-25343 19980218 (9) <--
PRIORITY: EP 1997-102547 19970218
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention refers to a nucleic acid construct comprising at least one activator sequence, at least one chimeric promoter module comprising a nucleotide sequence which binds a protein of the E2F family and a protein of the CDF-1 family, and at least one gene, wherein said chimeric promoter module promotes expression of the gene in the cell cycle later than the B-myb promoter but earlier than the cdc25C promoter. The invention also concerns the purification and identification of CDF-1 protein, and use of this protein to develop new control systems.

L27 ANSWER 14 OF 33 USPATFULL on STN
2001:208643 Induction of REV and TAT specific **cytotoxic** T-cells for **prevention** and treatment of **human immunodeficiency virus** (**HIV**) infection
.
Van Baalen, Carel A., Zeewolde, Netherlands
Osterhaus, Albertus D.M.E., Bunnik, Netherlands
Erasmus Universiteit Rotterdam, Rotterdam, Netherlands (non-U.S. corporation)
US 6319666 B1 20011120
WO 9817309 19980430
APPLICATION: US 1999-284651 19990617 (9) <--
WO 1997-IB1402 19971017 19990617 PCT 371 date 19990617 PCT 102(e) date
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The presence of **cytotoxic** T-cells to the Rev and/or Tat protein in samples from a subject infected with immunodeficiency virus, particularly **HIV** in humans, is an indication of a stable disease condition and a favorable prognosis of lack of progression to disease. **Immunogenic** compositions containing at least one **cytotoxic** T-cell epitope of the Rev and/or Tat protein of an immunodeficiency virus, particularly **HIV**, or a vector encoding the T-cell epitope, may be used to **prevent** infection by disease caused by the immunodeficiency virus, by stimulating, in the host, a specific **cytotoxic** T-cell response specific for the respective Rev and/or Tat proteins.

L27 ANSWER 15 OF 33 USPATFULL on STN
2001:208480 Detection and treatment of infections with immunoconjugates.
Goldenberg, M. David, Short Hills, NJ, United States
Immunomedics, Inc., Morris Plains, NJ, United States (U.S. corporation)
US 6319500 B1 20011120
APPLICATION: US 1993-158782 19931201 (8) <--
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method of targeting a diagnostic or therapeutic agent to a focus of infection comprises injecting a patient infected with a pathogen parenterally with an antibody conjugate which specifically binds to an accessible epitope of the pathogen or of a pathogen-associated antigen accreted at the focus of infection, the antibody conjugate further comprising a bound diagnostic or therapeutic agent for detecting, imaging or treating the infection. Polyspecific composite conjugates enhance the efficacy of the method, which is especially useful for treating infections that are refractory towards systemic chemotherapy.

L27 ANSWER 16 OF 33 USPATFULL on STN
2001:202380 Oligonucleotides which specifically bind retroviral nucleocapsid proteins.
Rein, Alan, Columbia, MD, United States
Casas-Finet, Jose, Gaithersburg, MD, United States
Fisher, Robert, Sharpsburg, MD, United States
Fivash, Matthew, Frederick, MD, United States
Henderson, Louis E., Mount Airy, MD, United States
The United States of America as represented by the Secretary of the Department of Health and Human Services, Washington, DC, United States (U.S. government)
US 6316190 B1 20011113
WO 9744064 19971127
APPLICATION: US 1999-180903 19990712 (9) <--
WO 1997-US8936 19970519 19990712 PCT 371 date 19990712 PCT 102(e) date<--
PRIORITY: US 1996-17128P 19960520 (60)
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention provides oligonucleotides which bind to retroviral nucleocapsid proteins with high affinity, molecular decoys for retroviral nucleocapsid proteins which inhibit viral replication, targeted molecules comprising high affinity oligonucleotides, assays for selecting test compounds, and related kits.

L27 ANSWER 17 OF 33 USPATFULL on STN
2001:158482 Method of eliminating inhibitory/instability regions of mRNA.
Pavlakis, George N., Rockville, MD, United States
Felber, Barbara K., Rockville, MD, United States
The United States of America as represented by the Department of Health and Human Services, Washington, DC, United States (U.S. corporation)
US 6291664 B1 20010918
APPLICATION: US 1999-414117 19991008 (9) <--
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method of locating an inhibitory/instability sequence or sequences within the coding region of an mRNA and modifying the gene encoding that mRNA to remove these inhibitory/instability sequences by making clustered nucleotide substitutions without altering the coding capacity of the gene is disclosed. Constructs containing these mutated genes and host cells containing these constructs are also disclosed. The method and constructs are exemplified by the mutation of a **Human Immunodeficiency Virus**-1 Rev-dependent gag gene to a Rev independent gag gene. Constructs useful in locating inhibitory/instability sequences within either the coding region or the 3' untranslated region of an mRNA are also disclosed. The exemplified constructs of the invention may also be useful in **HIV**-1 immunotherapy and immunoprophylaxis.

L27 ANSWER 18 OF 33 USPATFULL on STN
2001:75179 Nucleic acid constructs containing genes encoding transport signals.
Sedlacek, Hans-Harald, Marburg, Germany, Federal Republic of
Mueller, Rolf, Marburg, Germany, Federal Republic of
Luehrmann, Reinhard, Marburg, Germany, Federal Republic of
Aventis Pharma Deutschland GmbH, Frankfurt am Main, Germany, Federal Republic of (non-U.S. corporation)
US 6235526 B1 20010522
APPLICATION: US 1997-850744 19970502 (8) <--

PRIORITY: DE 1998-19817851 19980505
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Nucleic acid constructs are disclosed which possess a nuclear retention signal which is linked, downstream in the reading direction, to a transgene. The nuclear retention signal can regulate the presence of the transcription product in the cell nucleus or else the intracellular transport of the transcription product.

L27 ANSWER 19 OF 33 USPATFULL on STN
2000:101881 **Immunogenic** compositions comprising DAL/DAT double-mutant, auxotrophic, attenuated strains of Listeria and their methods of use.
Frankel, Fred R., Philadelphia, PA, United States
Portnoy, Daniel A., Albany, CA, United States
The Trustees of the University of Pennsylvania, Philadelphia, PA, United States (U.S. corporation)
US 6099848 20000808
APPLICATION: US 1997-972902 19971118 (8) <--
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Listeria monocytogenes is an intracellular bacterial pathogen that elicits a strong cellular immune response following infection and therefore has potential use as a **vaccine** vector. However, while infections by L. monocytogenes are fairly rare and can readily be controlled by a number of antibiotics, the organism can nevertheless cause meningitis and death, particularly in immunocompromised or pregnant patients. We therefore have endeavored to isolate a highly attenuated strain of this organism for use as a **vaccine** vector. D-Alanine is required for the synthesis of the mucopeptide component of the cell walls of virtually all bacteria and is found almost exclusively in the microbial world. We have found in L. monocytogenes two genes that control the synthesis of this compound, an alanine racemase gene (dal) and a D-amino acid aminotransferase gene (dat). By inactivating both genes, we produced an organism that could be grown in the laboratory when supplemented with D-alanine but was unable to grow outside the laboratory, particularly in the cytoplasm of eukaryotic host cells, the natural habitat of this organism during infection. In mice, the double-mutant strain was completely attenuated. Nevertheless, it showed the ability, particularly under conditions of transient suppression of the mutant phenotype, to induce **cytotoxic** T-lymphocyte responses and to generate **protective** immunity against lethal challenge by wild-type L. monocytogenes equivalent to that induced by the wild-type organism.

L27 ANSWER 20 OF 33 USPATFULL on STN
2000:101880 Chimeric Gag pseudovirions.
Tobin, Gregory J., Frederick, MD, United States
Gonda, Matthew A., Newtown Square, PA, United States
The United States of America as represented by the Department of Health and Human Services, Washington, DC, United States (U.S. government)
US 6099847 20000808
APPLICATION: US 1997-857385 19970515 (8) <--
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention provides, inter alia, recombinant chimeric nucleic acids encoding a Gag-fs-fusion partner fusion protein; a pseudovirion comprising a retroviral Gag protein and a fusion partner, wherein the fusion partner is present in a Gag-fs-fusion partner fusion protein; an **immunogenic** composition comprising a pseudovirion; a Gag-fs-fusion partner fusion protein; and a method of making the pseudovirions of the present invention.

L27 ANSWER 21 OF 33 USPATFULL on STN
2000:4680 Crossless retroviral vectors.
Respess, James G., San Diego, CA, United States
DePolo, Nicholas J., Solana Beach, CA, United States
Chada, Sunil, Missouri City, TX, United States

Sauter, Sybille, Del Mar, CA, United States
Bodner, Mordechai, San Diego, CA, United States
Driver, David A., San Diego, CA, United States
Chiron Corporation, Emeryville, CA, United States (U.S. corporation)
US 6013517 20000111
APPLICATION: US 1997-850961 19970505 (8) <--
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Retroviral vector constructs are described which have a 5' LTR, a tRNA binding site, a packaging signal, one or more heterologous sequences, an origin of second strand synthesis and a 3' LTR, wherein the vector construct lacks retroviral gag/pol or env coding sequences. In addition, gag/pol, and env expression-cassettes are described wherein the expression cassettes lack a consecutive sequence of more than 8 nucleotides in common. The above-described retroviral vector constructs, gag/pol and env expression cassettes may be utilized to construct producer cell lines which preclude the formation of replication competent virus.

L27 ANSWER 22 OF 33 USPATFULL on STN
1999:166852 Redirection of cellular immunity by protein tyrosine kinase chimeras.
Seed, Brian, Boston, MA, United States
Romeo, Charles, Belmont, MA, United States
Kolanus, Waldemar, Watertown, MA, United States
The Massachussetts General Hospital, Boston, MA, United States (U.S. corporation)
US 6004811 19991221
APPLICATION: US 1995-394912 19950224 (8) <--
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Disclosed is a method of directing a cellular response in a mammal by expressing in a cell of the mammal a chimeric receptor which causes the cells to specifically recognize and destroy an infective agent, a cell infected with an infective agent, a tumor or cancerous cell, or an autoimmune-generated cell. The chimeric receptor includes an extracellular portion which is capable of specifically recognizing and binding the target cell or target infective agent, and (b) an intracellular portion of a protein-tyrosine kinase which is capable of signalling the therapeutic cell to destroy a receptor-bound target cell or a receptor-bound target infective agent. Also disclosed are calls which express the chimeric receptors and DNA encoding the chimeric receptors.

L27 ANSWER 23 OF 33 USPATFULL on STN
1999:125062 Method of eliminating inhibitory/ instability regions of mRNA.
Pavlakis, George N., Rockville, MD, United States
Felber, Barbara K., Rockville, MD, United States
The United States of America as represented by the Department of Health and Human Services, Washington, DC, United States (U.S. government)
US 5965726 19991012
APPLICATION: US 1997-850049 19970502 (8) <--
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method of locating an inhibitory/instability sequence or sequences within the coding region of an mRNA and modifying the gene encoding that mRNA to remove these inhibitory/instability sequences by making clustered nucleotide substitutions without altering the coding capacity of the gene is disclosed. Constructs containing these mutated genes and host cells containing these constructs are also disclosed. The method and constructs are exemplified by the mutation of a **Human Immunodeficiency Virus**-1 Rev-dependent gag gene to a Rev-independent gag gene. Constructs useful in locating inhibitory/instability sequences within either the coding region or the 3' untranslated region of an mRNA are also disclosed. The exemplified constructs of the invention may also be useful in HIV-1 immunotherapy and immunoprophylaxis.

L27 ANSWER 24 OF 33 USPATFULL on STN
1999:117339 Chimeric antiviral agents comprising Rev binding nucleic acids and trans-acting ribozymes, and molecules encoding them.
Kraus, Gunter, Miami, FL, United States
Wong-Staal, Flossie, San Diego, CA, United States
Yu, Mang, San Diego, CA, United States
Yamada, Osamu, Kobe, Japan
The Regents of the University of California, Oakland, CA, United States (U.S. corporation)
US 5958768 19990928
APPLICATION: US 1996-697324 19960823 (8) <--
PRIORITY: US 1995-2793P 19950825 (60)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Methods and compositions for the treatment and diagnosis of infections of Rev-binding primate lentiviruses are provided. These methods and compositions utilize the ability of Rev binding nucleic acids such as the SLII sequence from the **HIV**-1 Rev response element (RRE) to target therapeutic agents to the same sub-cellular location as primate lentiviruses which contain RRE sequences. In particular, the invention provides trans-acting ribozymes comprising Rev-binding nucleic acids less toxic than a full-length RRE, and molecules encoding them. The use of the compositions of the invention as components of diagnostic assays, as prophylactic reagents, and in vectors is also described.

L27 ANSWER 25 OF 33 USPATFULL on STN
1999:109965 Induction of CTLs specific for natural antigens by cross priming immunization.
Falo, Jr., Louis D., Pittsburgh, PA, United States
Rock, Kenneth L., Chestnut Hill, MA, United States
University of Pittsburgh, Pittsburgh, PA, United States (U.S. corporation)Dana-Farber Cancer Institute, Boston, MA, United States (U.S. corporation)
US 5951975 19990914
APPLICATION: US 1996-675332 19960628 (8) <--
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to prophylactic and therapeutic methods of anti-tumor immunization. These methods are based on cross-priming a mammalian host to natural MHC class I restricted tumor antigens with an artificial tumor antigen. A primary tumor is resected from the patient and a population of tumor cells are cultured in vitro. These cultured tumor cells are loaded with an artificial target antigen. The loaded tumor cells are inactivated and introduced into the patient either simultaneous or subsequent to a direct immunization of the patient with the same or substantially the same artificial target antigen. This method of coupled host immunization promotes a tumor specific **cytotoxic** T lymphocyte (**CTL**) immune response against multiple, undefined natural tumor antigens expressed on the unmodified tumor cell surface.

L27 ANSWER 26 OF 33 USPATFULL on STN
1999:85264 Vectors for gene delivery.
Efstathiou, Stacey, 18 Norwich Street, Cambridge, United Kingdom CB2 1NE
Inglis, Stephen C., 2 Rhugarye Gardens, Linton, Cambridge, United Kingdom CB1 6LX
Zhang, Xiaoliu, 21 Oak Tree Avenue, Cambridge, United Kingdom CB4 1AZ
US 5928913 19990727
APPLICATION: US 1996-621501 19960325 (8) <--
PRIORITY: GB 1995-5892 19950323
US 1995-29P 19950608 (60)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Herpesvirus amplicon preparations comprise an origin of replication, a packaging sequence, and at least one inserted gene under control of a

promoter, suitable for use as an **immunogen** or **vaccine**, in
association with helper herpesvirus or DNA, wherein the associated
helper virus is of restricted replication competence in a normal host
cell; for example where the associated helper virus has an inactivating
defect in respect of a gene essential for production of infectious new
virus particles, and where the amplicon carries an inserted gene
necessary for the propagation of the helper virus.

L27 ANSWER 27 OF 33 USPATFULL on STN
1999:69784 Desmin enhancer sequences, vectors comprising these sequences and
their uses in compositions for the expression of nucleotide sequences in
transfected cells.
Paulin, Denise, Vincennes, France
Li, Zhen Lin, Paris, France
Institut Pasteur, Paris Cedex, France (non-U.S. corporation)Universite
Paris 7, Paris Cedex, France (non-U.S. corporation)
US 5914395 19990622
WO 9626284 19960829
APPLICATION: US 1997-894228 19970912 (8) <--
WO 1996-FR261 19960216 19970912 PCT 371 date 19970912 PCT 102(e) date<--
PRIORITY: FR 1995-1937 19950220
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention teaches modified desmin enhancer sequences which yield
high level expression of operably linked DNA sequences. The claimed
modified desmin enhancer sequences may be operably linked to genes
encoding a protein. Further these modified desmin enhancer sequences may
be placed into vectors including plasmids and transformed into cells
including bacteria or myoblasts. Finally, these modified desmin
enhancers may be used in methods of expression of proteins in the
transformed bacteria or myoblasts.

L27 ANSWER 28 OF 33 USPATFULL on STN
1999:4042 Anti-acids secretory recombinant BCG **vaccine**.
Matsuo, Kazuhiro, Kawasaki, Japan
Chujo, Yoshitomo, Kawasaki, Japan
Yamazaki, Akihiro, Kawasaki, Japan
Honda, Mitsuo, Mitaka, Japan
Yamazaki, Shudo, Higashiyamato, Japan
Tasaka, Hiromichi, Kure, Japan
Ajinomoto Co., Inc., Tokyo, Japan (non-U.S. corporation)Japan as
represented by Director General of Agency of National Institute of Health,
Tokyo, Japan (non-U.S. corporation)
US 5858369 19990112
APPLICATION: US 1997-975699 19971121 (8) <--
PRIORITY: JP 1994-178462 19940729
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A **vaccine** containing Mycobacterium bovis BCG which secretes a fusion
protein to be obtained by inserting a foreign antigen peptide into the
molecular surface of a secretory protein, a carrier, having a signal
peptide. BCG constituting the present invention secretes a fusion
protein to be obtained by inserting a foreign antigen peptide into the
molecular surface of an α-antigen derived from mycobacteria. Said
fusion protein has significantly increased antigenicity and
immunogenicity. Therefore, when it is inoculated into animals, it is
efficiently recognized by B cells which recognize said antigen, thereby
effectively inducing the production of an antibody to said antigen. When
said BCG itself is inoculated into animals, it continuously secretes
said fusion protein in the bodies of the animals while continuously
propagating therein. Therefore, said BCG is an extremely useful **vaccine**.

L27 ANSWER 29 OF 33 USPATFULL on STN
1998:138699 Method for production of high titer virus and high efficiency
retroviral mediated transduction of mammalian cells.
Finer, Mitchell H., San Carlos, CA, United States

Roberts, Margo R., San Francisco, CA, United States
Dull, Thomas J., San Francisco, CA, United States
Zsebo, Krisztina M., Woodside, CA, United States
Qin, Lu, Foster City, CA, United States
Farson, Deborah A., Oakland, CA, United States
Cell Genesys, Inc., Foster City, CA, United States (U.S. corporation)
US 5834256 19981110
APPLICATION: US 1993-76299 19930611 (8) <--
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention provides a novel retroviral packaging system, in which retroviral packaging constructs and packagable vector transcripts are produced from high expression plasmids by transfection in human cells. High titers of recombinant retrovirus are produced in infected cells. The methods of the invention include the use of the novel retroviral constructs to transduce primary human cells, including T cells and bone marrow stem cells, with foreign genes by cocultivation at high efficiencies. The invention is useful for the rapid production of high viral supernatants, and to transduce with high efficiency cells that are refractory to transduction by conventional means.

L27 ANSWER 30 OF 33 USPATFULL on STN
1998:58087 Peptides capable of inducing immune response to **HIV**.
Takiguchi, Masafumi, Tokyo, Japan
Miwa, Kiyoshi, Kawasaki, Japan
Ajinomoto Co., Inc., Tokyo, Japan (non-U.S. corporation)
US 5756666 19980526
WO 9511255 19950427
APPLICATION: US 1996-615181 19960404 (8) <--
WO 1994-JP1756 19941019 19960404 PCT 371 date 19960404 PCT 102(e) date
PRIORITY: JP 1993-261302 19931019
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Herein disclosed is a peptide which is a fragment of the whole protein of **HIV**, the fragment being a peptide having a sequence of successive 8 to 11 amino acid residues, which corresponds to an HLA-binding motif, which actually binds to HLA and which can induce killer cells capable of attacking **HIV**-infected cells as target cells. The peptide is effective as an anti-AIDS agent for **preventing** and curing AIDS.

L27 ANSWER 31 OF 33 USPATFULL on STN
1998:17356 Method of potentiating cell-mediated immunity utilizing polyamine derivatives.
Bowlin, Terry L., Maineville, OH, United States
Prakash, Nellikunja J., Cincinnati, OH, United States
Merrell Pharmaceuticals, Inc., Cincinnati, OH, United States (U.S. corporation)
US 5719193 19980217
APPLICATION: US 1995-422751 19950414 (8) <--
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention relates to a method of potentiating cell-mediated immunity which comprises administering to a patient a cell-mediated immunity potentiating amount of a compound of the formula:

$RHN{-}{-}Z{-}{-}NH{-}{-}(CH_2)_m{-}{-}NH{-}{-}Z{-}{-}NHR$

or a pharmaceutically acceptable salt thereof, wherein m is an integer 3 to 12, Z is a saturated C_2 -C_6 alkylene moiety of straight or branched chain configuration, each R group is independently H, a C_1 -C_6 saturated or unsaturated hydrocarbyl, or --$(CH_2)_x$ --(Ar)--X wherein X is H, C_1 -C_6 alkoxy, halogen, C_1 -C_4 alkyl, or --$S(O)_x R_1$, x is an integer 0, 1 or 2, and R_1 is C_1 -C_6 alkyl.

L27 ANSWER 32 OF 33 USPATFULL on STN
96:116263 Autonomous parvovirus gene delivery vehicles and expression vectors.
Maxwell, Ian H., Denver, CO, United States
Carlson, Jonathan, Ft. Collins, CO, United States
Corsini, Joseph A., Ft. Collins, CO, United States
Maxwell, Fran.cedilla.oise, Denver, CO, United States
Rhode, Solon L., Omaha, NE, United States
University of Colorado Foundation, Inc., Boulder, CO, United States (U.S. corporation)
US 5585254 19961217
APPLICATION: US 1993-42419 19930402 (8) <--
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to novel recombinant autonomous parvovirus vectors, novel recombinant virus particles, and novel gene delivery vehicles that can be used to selectively target heterologous nucleic acid sequences to desired cell types and to selectively express such sequences in such desired cell types. Recombinant autonomous parvovirus gene delivery vehicles are particularly advantageous for transient gene therapy, and are especially well-suited to treat diseases in which there is rapid cell growth, such as cancer. Also included is the use of recombinant vectors of the present invention to produce RNA and protein products in cell culture.

L27 ANSWER 33 OF 33 USPATFULL on STN
96:96943 **HIV**-3 retrovirus and its use.
De Leys, Robert, Grimbergen, Belgium
Vanderborght, Bart, Geel, Belgium
Saman, Eric, Niklaas, Belgium
Van Heuverswyn, Hugo, Laarne, Belgium
Innogenetics N.V., Belgium (non-U.S. corporation)
US 5567603 19961022
APPLICATION: US 1994-228519 19940415 (8) <--
PRIORITY: EP 1988-109200 19880609
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Described is a new retrovirus designated **HIV**-3, samples of which have been deposited in the European Collection of Animal Cell Cultures (ECACC) under V88060301. The morphological and immunological properties exhibited by the **HIV**-3 retrovirus class include:

a diameter of approximately 120 nm; a tropism for T4 lymphocytes; cultivation in T4 receptor-bearing immortalized cell lines; cytotoxicity for the lymphocytes that it infects; a magnesium dependent reverse transcriptase activity;

the genomic RNA of **HIV**-3 hybridizes neither with the sequences of **HIV**-1 nor with the sequences of **HIV**-2 under stringent hybridization conditions;

lysates of the virus contain a p25 protein which is immunologically distinct from the p19 protein of HTLV-I and the p24 proteins of **HIV**-1 and **HIV**-2 as determined by Western blot analysis, respectively;

lysates of the virus contain a gp120 protein which is immunologically distinct from the gp110 protein of HTLV-I, the gp120 of **HIV**-1 and the gp120 of **HIV**-2 as determined by Western blot analysis;

the lysate of the virus contains in addition a gp41 glycoprotein with a molecular weight of 40,000-45,000; and

lysates of the virus contain a p12 protein which is immunologically distinct from the p12 proteins of **HIV**-1 and **HIV**-2 as determined by Western blot analysis.

Also described are nucleic acid sequences derived from **HIV**-3 RNA which

can be used as hybridization probes to detect the presence of HIV 3
virus.

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L27 ANSWER 1 OF 33 USPATFULL on STN
2004:7101 REDIRECTION OF CELLULAR IMMUNITY BY RECEPTOR CHIMERAS.
SEED, BRIAN, BOSTON, MA, UNITED STATES
ROMEO, CHARLES, BELMONT, MA, UNITED STATES
KOLANUS, WALDEMAR, WATERTOWN, MA, UNITED STATES
US 2004005334 A1 20040108
APPLICATION: US 1999-243008 A1 19990202 (9) <--
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Disclosed is a method of directing a cellular response in a mammal by expressing in a cell of the mammal a chimeric receptor which causes the cells to specifically recognize and destroy an infective agent, a cell infected with an infective agent, a tumor or cancerous cell, or an autoimmune-generated cell. Also disclosed are cells which express the chimeric receptors and DNA encoding the chimeric receptors.

CLM What is claimed is:

1. A method of directing a cellular immune response in a mammal, said method comprising administering to said mammal an effective amount of therapeutic cells, said therapeutic cells expressing a membrane-bound, proteinaceous chimeric receptor comprising (a) an extracellular portion which is capable of specifically recognizing and binding said target cell or said target infective agent, and (b) an intracellular portion which is capable of signalling said therapeutic cell to destroy a receptor-bound target cell or a receptor-bound target infective agent.

2. The method of claim 1, wherein said target cell is a host cell infected with an infective agent, a tumor or cancerous cell, or an autoimmune-generated cell.

3. The method of claim 1, wherein said cellular response is MHC-independent.

4. The method of claim 1, wherein said intracellular portion is the signal-transducing portion of a T cell receptor protein, a B cell receptor protein, or an Fc receptor protein, or a functional derivative thereof.

5. The method of claim 1, wherein said chimeric receptor further comprises a transmembrane portion of said T cell receptor protein, said B cell receptor protein, or said Fc receptor protein.

6. A method of directing a cellular immune response in a mammal, said method comprising administering to said mammal an effective amount of therapeutic cells, said therapeutic cells expressing a membrane-bound, proteinaceous chimeric receptor, said receptor comprising (a) an extracellular portion which is capable of specifically recognizing and binding said target cell or said target infective agent, and (b) a transmembrane portion which is capable of signalling said therapeutic cell to destroy a receptor-bound target cell or a receptor-bound target infective agent.

7. The method of claim 6, wherein, following binding of said extracellular portion to said agent or said cell, said transmembrane portion oligomerizes with a cytolytic signal-transducing protein of said therapeutic cell resulting in destruction of said receptor-bound cell or agent.

8. The method of claim 6, wherein said transmembrane portion comprises an oligomerizing portion of a T cell receptor protein, a B cell receptor protein, or an Fc receptor protein, or a functional derivative thereof.

9. The method of claim 4, wherein said T cell receptor protein is ζ.

10. The method of claim 9, wherein said chimeric receptor comprises amino acids 421-532 of SEQ ID NO: 6, or a functional cytolytic signal-transducing derivative thereof.

11. The method of claim 9, wherein said chimeric receptor comprises amino acids (a) 423-455; (b) 438-455; (c) 461-494; or (d) 494-528 of SEQ ID NO: 6.

12. The method of claim 8, wherein said T cell receptor protein is ζ.

13. The method of claim 12, wherein said chimeric receptor comprises amino acids 400-420 of SEQ ID NO: 6.

14. The method of claim 4, wherein said T cell receptor protein is η.

15. The method of claim 14, wherein said chimeric receptor comprises amino acids 421-575 of SEQ ID NO: 4, or a functional cytolytic signal-transducing derivative thereof.

16. The method of claim 14, wherein said chimeric receptor comprises amino acids (a) 423-455; (b) 438-455; (c) 461-494; or (d) 494-528 of SEQ ID NO: 4.

17. The method of claim 8, wherein said T cell receptor protein is η.

18. The method of claim 17, wherein said chimeric receptor comprises amino acids 400-420 of SEQ ID NO: 4.

19. The method of claim 4, wherein said Fc receptor protein is γ.

20. The method of claim 19, wherein said chimeric receptor comprises amino acids 421-462 of SEQ ID NO:5, or a functional cytolytic signal-transducing derivative thereof.

21. The method of claim 8, wherein said Fc receptor protein is γ.

22. The method of claim 21, wherein said chimeric receptor comprises amino acids 402-419 of SEQ ID NO:5.

23. The method of claim 21, wherein said chimeric receptor comprises amino acids Tyr282-Tyr298 inclusive of FIG. 15A.

24. The method of claim 4 or 8, wherein said Fc receptor protein is human FcγRIII, human FcRIIγA, or human FcRIIγC.

25. The method of claim 4 or 8, wherein said T cell receptor protein is CD3 delta.

26. The method of claim 25, wherein said chimeric receptor protein comprises amino acids 132-171 of FIG. 16 (SEQ ID NO: 24).

27. The method of claim 4 or 8, wherein said T cell receptor protein is T3 gamma.

28. The method of claim 27, wherein said chimeric receptor protein comprises amino acids 140-182 of FIG. 17 (SEQ ID NO: 25).

29. The method of claim 4 or 8, wherein said B cell receptor protein is

NO:1.

30. The method of claim 29, wherein said chimeric receptor protein comprises amino acids 162-220 of FIG. 18 (SEQ ID NO: 26).

31. The method of claim 4 or 8, wherein said B cell receptor protein is B29.

32. The method of claim 31, wherein said chimeric receptor protein comprises amino acids 183-228of FIG. 19 (SEQ ID NO: 27).

33. The method of claim 1 or 6, wherein said therapeutic cells are selected from the group consisting of: (a) T lymphocytes; (b) **cytotoxic** T lymphocytes: (c) natural killer cells; (d) neutrophils; (e) granulocytes; (f) macrophages; (g) mast cells; (h) HeLa cells; and (i) embryonic stem cells (ES).

34. The method of claim 1 or 6, wherein said target infective agent is an immunodeficiency virus.

35. The method of claim 1 or 6, wherein said extracellular portion comprises an **HIV** envelope-binding portion of CD4, or a functional **HIV** envelope-binding derivative thereof.

36. The method of claim 1 or 6, wherein said **HIV**-envelope binding portion of CD4 comprises the peptide encoded by nucleotides 1-369 of SEQ ID NO:1.

37. The method of claim 1 or 6, wherein said therapeutic cells further express a membrane-bound, proteinaceous chimeric receptor comprising (a) an extracellular portion which is capable of specifically recognizing and binding said target cell or said target infective agent, and (b) an intracellular portion which is derived from CD28.

38. The method of claim 1 or 6, wherein said therapeutic cells destroy said receptor-bound target cell or target infective agent by cytolysis.

39. A cell which expresses a proteinaceous membrane-bound chimeric receptor, said receptor comprising (a) an extracellular portion which is capable of specifically recognizing and binding a target cell or a target infective agent, and (b) an intracellular portion derived from a T cell receptor, a B cell receptor, or an Fc receptor which is capable of signalling said cell to destroy a receptor-bound target cell or receptor-bound target infective agent.

40. The cell of claim 39, wherein said target cell is a host cell infected with an infective agent, a tumor or cancerous cell, or an autoimmune-generated cell.

41. The cell of claim 39, wherein said binding is MHC-independent.

42. The cell of claim 39, wherein said intracellular portion is the signal-transducing portion of a T cell receptor protein, a B cell receptor protein, or an Fc receptor protein, or a functional derivative thereof.

43. The cell of claim 42, wherein said chimeric receptor further comprises a transmembrane portion of said T cell receptor protein, said B cell receptor protein, or said Fc receptor protein.

44. A cell expressing a proteinaceous membrane-bound chimeric receptor, said receptor comprising (a) an extracellular portion which is capable of specifically recognizing and binding a target cell or a target infective agent, and a transmembrane portion derived from a T cell receptor, a B cell receptor, or an Fc receptor which is capable of signalling said cell to destroy a receptor-bound target cell or a

receptor bound target infective agent.

45. The cell of claim 44, wherein, following binding of said extracellular portion to said cell or agent, said transmembrane portion oligomerizes with a cytolytic signal-transducing protein of said receptor-bearing cell resulting in destruction of said receptor-bound agent or cell.

46. The cell of claim 44, wherein said binding is MHC-independent.

47. The cell of claims 44, wherein said transmembrane portion comprises an oligomerizing portion of a T cell receptor protein, a B cell receptor protein, or an Fc receptor protein, or a functional derivative thereof.

48. The cell of claim 42, wherein said T cell receptor protein is ζ.

49. The cell of claim 48, wherein said chimeric receptor comprises amino acids 421-532 of SEQ ID NO: 6, or a functional cytolytic signal-transducing derivative thereof.

50. The cell of claim 48, wherein said chimeric receptor comprises amino acids (a) 423-455; (b) 438-455; (c) 461-494; or (d) 494-528 of SEQ ID NO. 6.

51. The cell of claim 47, wherein said T cell receptor protein is ζ.

52. The cell of claim 51, where in said chimeric receptor comprises amino acids 400-420 of SEQ ID NO: 6.

53. The cell of claim 42, wherein said T cell receptor protein is η.

54. The cell of claim 53, wherein said chimeric receptor comprises amino acids 421-575 of SEQ ID NO: 4, or a functional cytolytic signal-transducing derivative thereof.

55. The cell of claim 53, wherein said chimeric receptor comprises amino acids (a) 423-455; (b) 438-455; (c) 461-494; or (d) 494-528 of SEQ ID NO: 4.

56. The cell of claim 47, wherein said T cell receptor protein is η.

57. The cell of claim 56, wherein said chimeric receptor comprises amino acids 400-420 of SEQ ID NO: 4.

58. The cell of claim 42, wherein said Fc receptor protein is γ.

59. The cell of claim 58, wherein said chimeric receptor comprises amino acids 421-462 of SEQ ID NO:5, or a functional cytolytic signal-transducing derivative thereof.

60. The cell of claim 47, wherein said Fc receptor protein is γ.

61. The cell of claim 60, wherein said chimeric receptor comprises amino acids 402-419 of SEQ ID NO: 5.

62. The cell of claim 60, wherein said chimeric receptor comprises amino acids Tyr282-Tyr298 inclusive of FIG. 15A.

63. The cell of claim 42 or 47, wherein said Fc receptor protein is human FcγRIII, human FcRIIγA, or human FcRIIγC.

64. The cell of claim 42 or 47, wherein said T cell receptor protein is CD3 delta.

65. The cell of claim 64, wherein said chimeric receptor protein comprises amino acids 132-171 of FIG. 16 (SEQ ID NO: 24).

66. The cell of claim 42 or 47, wherein said T cell receptor protein is T3 gamma.

67. The cell of claim 66, wherein said chimeric receptor protein comprises amino acids 140-182 of FIG. 17 (SEQ ID NO: 25).

68. The cell of claim 42 or 47, wherein said B cell receptor protein is mb1.

69. The cell of claim 68, wherein said chimeric receptor protein comprises amino acids 162-220 of FIG. 18 (SEQ ID NO: 26).

70. The cell of claim 42 or 47, wherein said B cell receptor protein is B29.

71. The cell of claim 70, wherein said chimeric receptor protein comprises amino acids 183-228 of FIG. 19 (SEQ ID NO: 27).

72. The cell of claim 39 or 44, wherein said extracellular portion comprises the ligand-binding portion of a receptor, the receptor-binding portion of a ligand, the antigen-binding portion of an antibody, or a functional derivative thereof.

73. The cell of claim 39 or 44, wherein said target infective agent is an immunodeficiency virus or said target cell is a host cell infected with an immunodeficiency virus.

74. The cell of claim 73, wherein said extracellular portion comprises an **HIV** envelope-binding portion of CD4, or a functional derivative thereof.

75. The cell of claim 73, wherein said **HIV**-envelope binding portion of CD4 comprises the peptide encoded by nucleotides 1-369 of SEQ ID NO:1.

76. The cell of claim 39 or 44, wherein said cell further expresses a membrane-bound, proteinaceous chimeric receptor comprising (a) an extracellular portion which is capable of specifically recognizing and binding said target cell or said target infective agent, and (b) an intracellular portion which is derived from CD28.

77. The cell of claim 39 or 44, wherein said cell destroys said receptor-bound target cell or target infective agent by cytolysis.

78. A cell which expresses a proteinaceous membrane-bound chimeric receptor, said receptor comprising (a) an extracellular portion which is capable of specifically recognizing and binding a target cell or a target infective agent, and (b) an intracellular portion derived from a T cell receptor CD3, zeta, or eta polypeptide, a B cell receptor, or an Fc receptor.

79. A cell which expresses a proteinaceous membrane-bound chimeric receptor, said receptor comprising (a) an extracellular portion which is capable of specifically recognizing and binding a target cell or a target infective agent, and (b) a transmembrane portion derived from a T cell receptor CD3, zeta, or eta polypeptide, a B cell receptor, or an Fc receptor.

80. The cell of claim 78 or 79, wherein said chimeric receptor includes a CD16 or CD5 extracellular portion.

81. The cell of claim 78 or 79, wherein said chimeric receptor includes a CD5 or CD7 transmembrane portion.

82. The cell of claim 78 or 79, wherein said chimeric receptor includes a CD5 or CD7 intracellular portion.

83. **DNA** encoding a proteinaceous membrane-bound chimeric receptor, said receptor comprising (a) an extracellular portion which is capable of specifically recognizing and binding a target cell or a target infective agent, and (b) an intracellular portion derived from a T cell receptor, a B cell receptor, or an Fc receptor which is capable of signalling said cell to destroy a receptor-bound target cell or receptor-bound target infective agent.

84. **DNA** encoding a proteinaceous membrane-bound chimeric receptor, said receptor comprising (a) an extracellular portion which is capable of specifically recognizing and binding a target cell or a target infective agent, and (b) a transmembrane portion derived from a T cell receptor, a B cell receptor, or an Fc receptor which is capable of signalling said cell to destroy a receptor-bound target cell or a receptor-bound target infective agent.

85. **DNA** encoding a proteinaceous membrane-bound chimeric receptor, said receptor comprising (a) an extracellular portion which is capable of specifically recognizing and binding a target cell or a target infective agent, and (b) an intracellular portion derived from a T cell receptor CD3, zeta, or eta polypeptide, a B cell receptor, or an Fc receptor.

86. **DNA** encoding a proteinaceous membrane-bound chimeric receptor, said receptor comprising (a) an extracellular portion which is capable of specifically recognizing and binding a target cell or a target infective agent, and (b) a transmembrane portion derived from a T cell receptor CD3, zeta, or eta polypeptide, a B cell receptor, or an Fc receptor.

87. **DNA** having a sequence substantially similar to the sequence shown in SEQ ID NO:1.

88. **DNA** having a sequence substantially similar to the sequence shown in SEQ ID NO:2.

89. **DNA** having a sequence substantially similar to the sequence shown in SEQ ID NO:3.

90. A vector comprising the chimeric receptor **DNA** of any of claims 83-86.

91. An antibody which specifically recognizes and binds a chimeric receptor of claim 39 or 44.

L27 ANSWER 2 OF 33 USPATFULL on STN
2003:314466 **HIV**-specific T-cell induction.
Sastry, K. Jagannadha, Bastrop, TX, United States
Arlinghaus, Ralph B., Bellaire, TX, United States
Nehete, Pramod N., Bastrop, TX, United States
Board of Regents, The University of Texas System, Austin, TX, United States (U.S. corporation)
US 6656471 B1 20031202
APPLICATION: US 1999-440772 19991116 (9) <--
PRIORITY: US 1998-108563P 19981116 (60)
US 1999-115175P 19990108 (60)
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention discloses diagnostic, **preventative**, and treatment therapies of AIDS involving determining whether a subject exhibits an HLA-Cw7-restricted **CTL** response. Some methods are directed to the use

of HLA-Cw7 as a genetic marker for long term non progression and amenability to treatment therapies. Diagnostic methods include a method for predicting long term non-progression in an **HIV**-infected subject. **Preventative** and treatment methods encompass determining whether a subject exhibits or can exhibit an HLA-Cw7-restricted **CTL** response. They also encompass ways of eliciting such a response, if necessary. Furthermore, some of the methods involve administering one or more **HIV** polypeptides or peptides, or polynucleotides encoding them, as a treatment therapy to **prevent** the development of AIDS.

CLM What is claimed is:

1. A method of treating an **HIV** infection in a human subject comprising administering to said subject a synthetic peptide composition comprising at least the sequence of SEQ ID NO:20, 21, 22, 23, 24, 25 or 40.

2. The method of claim 1, further comprising determining whether said subject exhibits an HLA-Cw7-restricted **CTL** response.

3. The method of claim 1, wherein synthetic **HIV** peptides of the composition comprise up to 50 residues.

4. The method of claim 3, wherein synthetic **HIV** peptides of the composition are 11 to 25 residues in length.

5. The method of claim 4, wherein said synthetic peptides are 11 to 25 residues in length and comprise the sequences: (a) SEQ ID NO:26, 27, 28, 29, 30, 31, 32, 33 or 34; (b) SEQ ID NO:20, 21, 22, 23, 24, 25 or 40; and (c) SEQ ID NO:1, 2 or 3.

6. The method of claim 1 wherein said composition is fixer defined as comprising a plurality of **HIV** peptides, wherein said composition further comprises an **HIV** peptide having the sequence: (a) SEQ ID NO:26, 27, 28, 29, 30, 31, 32, 33 or 34; or (b) SEQ ID NO:1, 2 or 3.

7. The method of claim 1, wherein the composition further comprises one or more synthetic peptides comprising the sequences: (a) SEQ ID NO:8, 9, 10, 11, 12, 13, 14, 15 or 38; or (b) SEQ ID NO:16, 17, 18, 19 or 39.

8. The method of claim 6, wherein the plurality of **HIV** peptides comprises three different peptides comprising, individually, the sequences: (a) SEQ ID NO:26, 27, 28, 29, 30, 31, 32, 33 or 34; (b) SEQ ID NO:20, 21, 22, 23, 24, 25 or 40; and (c) SEQ IM NO:1, 2 or 3.

9. The method of claim 8, wherein the plurality of **HIV** peptides comprises four different peptides comprising, individually, the sequences: (a) SEQ ID NO:26, 27, 28, 29, 30, 31, 32, 33 or 34; (b) SEQ ID NO:20, 21, 22, 23, 24, 25 or 40; (c) SEQ ID NO:1, 2 or 3; and (d) SEQ ID NO:4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 38, 16, 17, 18, 19 or 39.

10. The method of claim 9, wherein the plurality of **HIV** peptides comprises five different peptides comprising, individually, the sequences: (a) SEQ ID NO:26, 27, 28, 29, 30, 31, 32, 33 or 34; (b) SEQ ID NO:20, 21, 22, 23, 24, 25 or 40; (c) SEQ ID NO:1, 2 or 3; (d) SEQ ID NO:4, 5, 6 or 7; and (e) SEQ ID NO:8, 9, 10, 11, 12, 13, 14, 15, 38, 16, 17, 18, 19 or 39.

11. The method of claim 10, wherein the plurality of **HIV** peptides comprises six different peptides comprising, individually, the sequences: (a) SEQ ID NO:26, 27, 28, 29, 30, 31, 32, 33 or 34; (b) SEQ ID NO:20, 21, 22, 23, 24, 25 or 40; (c) SEQ ID NO:1, 2 or 3; (d) SEQ ID NO:4, 5, 6, or 7; (e) SEQ ID NO:8, 9, 10, 11, 12, 13, 14, 15 or 38; and (f) SEQ ID NO:16, 17, 18, 19 or 20.

12. The method of claim 1, wherein said **HIV** peptide or peptides are coupled to a carrier molecule.

13. The method of claim 12, wherein said carrier molecule is RNA or DNA.

14. The method of claim 1, wherein said composition further comprises an adjuvant.

15. The method of claim 14, wherein said adjuvant is selected from a group consisting of lipids, toxins, cytokines, oligonucleotides and bacterial **DNA**.

16. The method of claim 1, further comprising administering AZT to said subject.

17. The method of claim 1, further comprising carrying out HAART on said subject.

18. The method of claim 2, wherein the subject does not exhibit an HLA-Cw7-restricted **CTL** response, further comprising: (c) determining if the subject expresses the HLA-Cw7 haplotype; and if so, (d) eliciting said response.

19. The method of claim 18, wherein eliciting said response comprises administering to said subject a therapeutically effective amount of α- or γ-interferon, whereby the level of HLA-Cw7 haplotype expression increases.

20. The method of claim 18, wherein determining expression of the HLA-Cw7 haplotype comprises a serological assay using an antibody that recognizes an HLA-Cw7 epitope.

21. The method of claim 18, wherein determining expression of the HLA-Cw7 haplotype comprises performing a **nucleic acid** amplification reaction, wherein a region within the coding sequence of HLA-Cw7 is amplified.

22. The method of claim 1, wherein the **HIV** is **HIV**-1.

23. The method of claim 1, wherein the composition is injected into the subject intradermally or subcutaneously.

24. The method of claim 1, wherein the composition is administered more than one time.

25. The method of any claims 1, 2, 3-6, 7-22, 23, 24 wherein the treatment resulted in **preventing** an **HIV**-infected subject from developing AIDS.

L27 ANSWER 3 OF 33 USPATFULL on STN
2003:279110 Retrovirus and viral vectors.
Lauermann, Vit, Baltimore, MD, United States
Rubicon Laboratory, Inc., Baltimore, MD, United States (U.S. corporation)
US 6635472 B1 20031021
APPLICATION: US 1998-134360 19980814 (9) <--
PRIORITY: US 1997-55864P 19970815 (60)
US 1998-91734P 19980706 (60)
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention relates to the fields of genetic engineering, virus replication and gene transfer. More specifically, this invention relates to polynucleotide construct, recombinant virus, transposon, and their vectors, wherein an ori derived from a DNA virus capable of replicating in vertebrate cells is inserted into the retrovirus, allowing the retrovirus following the reverse transcription to efficiently replicate as extrachromosomal or episomal DNA without the necessity of integration into the host cell chromosome. Additionally, this invention relates to polynucleotide construct, recombinant virus, transposon, and their

vectors replicating episomally without aid of an ori and related elements. Also, this invention encompasses **preventive**, therapeutic, and diagnostic applications employing said constructs, viruses and vectors.

CLM What is claimed is:

1. A polynucleotide construct comprising retroviral sequence encoding at least one LTR, polypurine tract and packaging signal of a retroviral genome of an episomally replicating retrovirus, which is able to replicate without requirement of integration, said retroviral sequences further comprising one or more mutations that disable the integration of said construct into host chromosomal **DNA**, said construct further having the capacity to replicate via reverse transcription, provided that any reverse transcription product obtained from such reverse transcription is also disabled from integrating into host chromosomal **DNA**, said retroviral sequence further comprising a heterologous sequence encoding a gene product of interest.

2. The polynucleotide construct of claim 1 in which said retroviral sequence further comprise the 5' and 3' LTRs.

3. The polynucicotide construct of claim 1 in which said retroviral genome is selected from the group consisting of **HIV**, HTLV, MLV, AMV, ALV, BLV, SSV, RSV, CAEV, SIV, ERV, EAIV and FIV.

4. The polynucleotide construct of claim 1 in which said retroviral sequence further comprise an origin of **DNA** replication.

5. The polynucleotide construct of claim 4 in which said origin of **DNA** replication is one found in a **DNA** virus.

6. The polynucleotide construct of claim 5 in which said **DNA** virus is selected from the group consisting of papova viruses or herpes viruses.

7. The polynucleotide construct of claim 1 in which said one or more mutations are within an inverted repeat of a LTR or an integrase.

8. The polynucleotide construct of claim 1 which further comprise a capsid, polymerase, protease, integrase, envelope, auxiliary region, or combination of same.

9. The polynucleotide construct of claim 1 in which said heterologous sequence is a foreign gene.

10. The polynucleotide construct of claim 1 in which said heterologous sequence is a vertebrate gene.

11. The polynucleotide construct of claim 9 in which said foreign gene is either defective or absent from a host cell.

12. The polynucleotide construct of claim 1 in combination with retroviral genes carried by one or more helper constructs, wherein said combination encodes integration defective infectious virions.

13. A composition comprising retroviral sequence encoding all the genetic elements necessary for the production of an **immunogenic** virion, including one or more LTRs, said genetic elements including one or more mutations that disable the integration of viral **DNA** into host chromosomal **DNA**, such that any **DNA** molecules arising from a reverse transcription step involving an RNA of said **immunogenic** virion are able to exist episomally within host vertebrate cells, said virion further being able to replicate without requirement of integration, said retroviral sequence further comprising a heterologous sequence encoding a gene product of interest.

14. The retroviral sequence of claim 13 in which said episomal existence provides an **immunogenic** virion that can stimulate an immune system of

a vertebrate host.

15. The retroviral sequence of claim 13 in which said **immunogenic** virion is a retrovirus.

16. The composition of claim 15 in which said retrovirus is selected from the group consisting of MLV, AMV, ALV, BLV, SSV, RSV, CAEV, **HIV**, HTLV, SIV, ERV, EAIV, or FIV.

17. The composition of claim 13 which used in cancer cells.

18. The retroviral sequence of claim 13 which is able to exist episomally within selected cells of a vertebrate host.

19. The heterologous sequence of claim 13 which comprises nucleotide sequences encoding a cytokine or chemokine.

20. The heterologous sequence of claim 13 which comprises a gene encoding a protein that converts a pro-drug into a **cytotoxic** agent.

21. The heterologous sequence of claim 13 which comprises one or more tumor markers expressed in selected cells of a host into which said composition has been introduced.

22. The heterologous sequence of claim 21 which said one or more tumor markers are selected from the group consisting of a suppressor gene or an oncogene.

23. The heterologous sequence of claim 22 in which said suppressor gene is selected from a group consisting of p53, p73, p51, p40, or ket gene.

24. The heterologous sequence of claim 22 in which said oncogene is selected from a group consisting of c-myc, c-jun, c-fos, c-rel, c-qin, c-neu, c-src, c-abl, c-lck, c-mil/raf, c-ras, c-sis, or c-fps.

L27 ANSWER 4 OF 33 USPATFULL on STN
2003:196946 Immunodeficiency recombinant poxvirus.
Paoletti, Enzo, Delmar, NY, United States
Tartaglia, James, Schenectady, NY, United States
Cox, William I., East Greenbush, NY, United States
Gallo, Robert, Baltimore, MD, United States
Franchini, Genoveffa, Washington, DC, United States
Virogenetics Corporation, Troy, NY, United States (U.S. corporation)
US 6596279 B1 20030722
APPLICATION: US 1998-136159 19980814 (9) <--
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Attenuated recombinant viruses containing DNA encoding an immunodeficiency virus and/or **CTL** antigen, as well as methods and compositions employing the viruses, expression products therefrom, and antibodies generated from the viruses or expression products, are disclosed and claimed. The recombinant viruses can be NYVAC or ALVAC recombinant viruses. The DNA can code for at least one of: HIV1gag(+pro)(IIIB), gp120(MN)(+transmembrane), nef(BRU)**CTL**, pol(IIIB)**CTL**, ELDKWA or LDKW epitopes, preferably HIV1gag(+pro)(IIIB), gp120(MN) (+transmembrane), two (2) nef(BRU)**CTL** and three (3) pol(IIIB)**CTL** etpitopes; or two ELDKWA in gp120 V3 or another region or in gp160. The two (2) nef(BRU)**CTL** and three (3) pol(IIIB)**CTL** epitopes are preferably CTL1, CTL2, pol1, pol2 and pol3. The recombinant viruses and gene products therefrom and antibodies generated by the viruses and gene products have several **preventive**, therapeutic and diagnostic uses. DNA from the recombinant viruses are useful as probes or, for generating PCR primers or for immunization. Also disclosed and claimed are **HIV immunogens** and modified gp160 and gp120.

CLM What is claimed is:

1. A recombinant poxvirus comprising exogenous **DNA** encoding at least one Lentivirus epitope, wherein the poxvirus is a **vaccinia** virus having J2R, B13R+B14R, A26L, A56R, C7L-K1L and I4L are deleted from the virus; or a thymidine kinase gene, a hemorrhagic region, an A type inclusion body region, a hemagglutinin gene, a host range region, and a large subunit, ribonucleotide reductase are deleted from the virus; or the poxvirus is a NYVAC recombinant virus; and wherein the exogenous **DNA** encodes: HIV1 gag(+pro)(IIIB), gp120(MN)(+transmembrane) and two nef(BRU)**CTL** epitopes; or gp120(MN)(+transmembrane) and two ELDKWA (SEQ ID NO: 147) epitopes in the gp120 V3 loop region; or HIV1 gag(+pro)(IIIB) and gp120(MN)(+transmembrane); or HIV1 gag(+pro)(IIIB), gp120(MN)(+transmembrane) and two nef(BRU) and three pol(IIIB) **CTL** epitope containing regions; or at least one of: HIV1 gag(+pro)(IIIB), gp120(MN)(+transmembrane), nef(BRU)**CTL**, pol(IIIB)**CTL**, and ELDKWA (SEQ ID NO: 147) or LDKW (SEQ ID NO: 148) epitopes.

2. The recombinant poxvirus of claim 1 wherein wherein the exogenous **DNA** encodes HIV1 gag(+pro)(IIIB), gp120(MN)(+transmembrane) and two nef(BRU)**CTL** epitopes.

3. The recombinant poxvirus of claim 2 wherein the two nef(BRU)**CTL** epitopes are CTL1 and CTL2.

4. The recombinant poxvirus of claim 1 wherein the exogenous **DNA** encodes gp120(MN)(+transmembrane) and two ELDKWA (SEO ID NO: 147) epitopes in the gp120 V3 loop region.

5. The recombinant poxvirus of claim 1 wherein the exogenous **DNA** encodes HIV1 gag(+pro)(IIIB) and gp120(MN)(+transmembrane).

6. The recombinant poxvirus of claim 1 wherein the exogenous **DNA** encodes HIV1 gag(+pro)(IIIB), gp120(MN)(+transmembrane) and two nef(BRU) and three pol(IIIB) **CTL** epitope containing regions.

7. The recombinant poxvirus of claim 6 wherein the two nef(BRU)**CTL** and three pol(IIIB)**CTL** epitopes are: CTL1, CTL2, pol1, pol2 and pol3.

8. The recombinant poxvirus of claim 1 which is a NYVAC recombinant virus.

9. The recombinant poxvirus of claim 1 wherein the exogenous **DNA** codes for at least one of: HIV1 gag(+pro)(IIIB), gp120(MN)(+transmembrane), nef(BRU)**CTL**, pol(IIIB)**CTL**, and ELDKWA (SEQ ID NO: 147) or LDKW (SEQ ID NO: 148) epitopes.

10. The recombinant poxvirus of claim 9 wherein the exogenous **DNA** codes for HIV1 gag(+pro)(IIIB), gp120(MN)(+transmembrane), two nef(BRU)**CTL** and three pol(IIIB)**CTL** epitopes; or, two ELDKWA (SEO ID NO: 147) epitopes.

11. The recombinant poxvirus of claim 10 wherein the two nef(BRU)**CTL** and three pol(IIIB)**CTL** epitopes are: CTL1, CTL2, pol1, pol2 and pol3.

12. The recombinant poxvirus of claim 9 wherein the ELDKWA (SEQ ID NO: 147) or LDKW (SEQ ID NO: 148) epitopes are expressed as part of a region of gp120 or a region of gp160.

13. The virus of claim 12 wherein the ELDKWA (SEQ ID NO: 147) or LDKW (SEQ ID NO: 148) epitopes are expressed as part of gp120 V3.

14. A recombinant poxvirus which is vP1313.

15. A **immunogenic** composition comprising a recombinant poxvirus as claimed in claim 1 and a carrier.

16. A method for expressing a Lentivirus gene product comprising

infecting a suitable host cell with a recombinant poxvirus as claimed in claim 1.

17. A method for inducing an immunogical response to a Lentivirus gene product comprising administering a recombinant poxvirus as claimed in claim 1.

18. A method for inducing an immunogical response to a Lentivirus gene product comprising administering a composition as claimed in claim 15.

19. A method for inducing an immunogical response to a Lentivirus gene product comprising administering a recombinant poxvirus comprising exogenous **DNA** encoding at least one Lentivirus epitope, wherein the poxvirus is a **vaccinia** virus having J2R, B13R+B14R, A26L, A56R, C7L-K1L and I4L are deleted from the virus; or a thymidine kinase gene, a hemorrhagic region, an A type inclusion body region, a hemagglutinin gene, a host range region, and a large subunit, ribonucleotide reductase are deleted from the virus; or the poxvirus is a NYVAC recombinant virus; and said method further comprising subsequently administering an antigen derived from a Lentivirus, whereby the administation of the recombinant poxvirus is a priming administration and the administration of the antigen derived from the Lentivirus is a booster administration.

20. The method of claim 18 further comprising subsequently administering an antigen derived from Lentivirus, whereby the administation of the composition is a priming administration and the administration of the antigen derived from Lentivirus is a booster administration.

21. The method of claim 19 wherein the Lentivirus is **human immunodeficiency virus**.

22. A recombinant poxvirus which is vP1319.

23. The method of claim 17 further comprising subsequently administering an antigen derived from Lentivirus, whereby the administation of the composition is a priming administration and the administration of the antigen derived from Lentivirus is a booster administration.

L27 ANSWER 5 OF 33 USPATFULL on STN
2003:129925 Use of immunopotentiating sequences for inducing immune response.
McMillan, Minnie, Bradbury, CA, United States
University of Southern California, Los Angeles, CA, United States (U.S. corporation)
US 6562800 B1 20030513
APPLICATION: US 1999-430470 19991029 (9) <--
PRIORITY: US 1998-106506P 19981030 (60)
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides an **immunogenic** composition comprising a DNA expression vector encoding both an immunopotentiating chemokine sequence as well as an **immunogenic** polypeptide sequence. **Immunogenic** polypeptide sequences are those of infectious agents or of cancerous cells. Also provided are methods of manufacturing various **immunogenic** compositions, and methods of using such compositions to treat cancer and infectious disease.

CLM What is claimed is:

1. A **DNA** expression vector for inducing an immune response comprising: a first **DNA** sequence encoding an immunopotentiating chemokine fragment comprising the sequence of SEQ ID NO:22, said fragment having a length that is not more than 10% of the source immunopotentiating chemokine; and a second **DNA** sequence encoding a heterologous **immunogenic** polypeptide.

2. The **DNA** expression vector of claim 1 wherein the immunopotentiating chemokine fragment is a chemokine fragment that attracts T cells.

3. The **DNA** expression vector of claim 1 wherein the immunopotentiating chemokine fragment is a chemokine fragment that attracts cells of the monocyte lineage.

4. The **DNA** expression vector of claim 1 wherein the immunopotentiating chemokine fragment is a chemokine fragment that attracts B cells.

5. The **DNA** expression vector of claim 1 wherein the **DNA** expression vector further comprises a third **DNA** sequence encoding a hydrophobic leader signalling motif that directs the import of the **immunogenic** polypeptide into the endoplasmic reticulum of an antigen presenting cell.

6. The **DNA** expression vector of claim 5 wherein the **DNA** expression vector further comprises a fourth **DNA** sequence encoding a signalling motif for retaining the **immunogenic** polypeptide within the endoplasmic reticulum of an antigen presenting cell.

7. The **DNA** expression vector of claim 6 wherein the **DNA** expression vector further comprises a fifth **DNA** sequence encoding a signalling motif for sending the **immunogenic** polypeptide into the MHC Class II pathways of an antigen presenting cell.

8. The **DNA** expression vector of claim 1 wherein the **immunogenic** polypeptide is the gp120 IIIB coat protein of the **HIV** virus.

9. The **DNA** expression vector of claim 1 wherein the **immunogenic** polypeptide is the AG85A protein from the Mycobacterium tuberculosis.

10. The **DNA** expression vector of claim 1 wherein the **DNA** expression vector is selected from the group consisting of plasmids, adenovirus vectors, poxivirus vectors, adenoassociated virus vectors, and retrovirus vectors.

11. The **DNA** expression vector of claim 10 wherein the vector comprises the sequence of SEQ ID NO:1 or SEQ ID NO:3.

12. The **DNA** expression vector of claim 1 wherein the **immunogenic** polypeptide is a **cytotoxic** T lymphocyte epitope.

13. The **DNA** expression vector of claim 1 wherein the **immunogenic** polypeptide is a B cell epitope.

14. The **DNA** expression vector of claim 12 further comprising a sequence encoding a T helper cell epitope.

15. The **DNA** expression vector of claim 13 further comprising a sequence encoding a T helper cell epitope.

16. A composition for inducing an immune response comprising: an effective amount of the **DNA** expression vector of claim 1 and a carrier.

17. A method of manufacturing a composition for inducing an immune response comprising: combining an effective amount of the **DNA** expression vector of claim 1 and a carrier.

L27 ANSWER 6 OF 33 USPATFULL on STN
2003:74293 **Vaccines** comprising synthetic genes.
Shiver, John W., Doylestown, PA, United States
Davies, Mary Ellen, Norristown, PA, United States
Freed, Daniel C., King of Prussia, PA, United States
Liu, Margaret A., Rosemont, PA, United States
Perry, Helen C., Lansdale, PA, United States
Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)

US 6534312 B1 20030318

APPLICATION: US 1999-340798 19990628 (9) <--

PRIORITY: US 1996-20166P 19960621 (60)

US 1996-20165P 19960621 (60)

US 1996-12082P 19960222 (60)

DOCUMENT TYPE: Utility; GRANTED.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Synthetic polynucleotides comprising a DNA sequence encoding a peptide or protein are provided. The DNA sequence of the synthetic polynucleotides comprise codons optimized for expression in a nonhomologous host. The invention is exemplified by synthetic DNA molecules encoding **HIV** env as well as modifications of **HIV** env. The codons of the synthetic molecules include the projected host cell's preferred codons. The synthetic molecules provide preferred forms of foreign genetic material. The synthetic molecules may be used as a polynucleotide **vaccine** which provides immunoprophylaxis against **HIV** infection through neutralizing antibody and cell-mediated immunity. This invention provides polynucleotides which, when directly introduced into a vertebrate in vivo, including mammals such as primates and humans, induces the expression of encoded proteins within the animal.

CLM What is claimed is:

1. A synthetic polynucleotide comprising a **DNA** sequence encoding **HIV** env protein or a fragment thereof, the **DNA** sequence comprising codons optimized for expression in a mammalian host, wherein said synthetic polynucleotide is selected from the group consisting of: a) V1Jns-tPA-**HIV**$_{MN}$ gp120, wherein the 5' end which is SEQ ID NO:4 and the 3' end which is SEQ ID NO:5; b) V1Jns-tPA-**HIV**$_{IIIB}$ gp120, wherein the 5' end which is SEQ ID NO:6 and the 3' end which is SEQ ID NO:7; c) V1Jns-tPA-gp160/opt C1/opt41-A and V1Jns-tPA-gp160/opt C1/opt41-B, wherein the opt C1 comprises SEQ ID NO:30, and the gp120/41 proteolytic cleavage sites is retained in the "B" form (SEQ ID NO:33) and eliminated in the "A" form (SEQ ID NO:32); d) V1Jns-tPA-gp160/opt all-A, V1Jns-tPA-gp160/opt all-B, V1Jns-tPA gp160/opt all-A (non$_{IIIB}$ strains); V1Jns-tPA-gp160/opt all-B (non$_{IIIB}$ strains), wherein the optimized codon usage is derived from opt C1 (SEQ ID NO:30), and wherein the gp160 proteolytic cleavage site is retained in form "B" (SEQ ID NO:33) and is eliminated in form "A" (SEQ ID NO:32); e) V1Jns-tPA-gp143, V1Jns-tPA-gp143/mutRRE-A, and V1Jns-tPA-gp143/mutRRE-B, wherein the gp160 proteolytic cleavage site is retained in form "B" (SEQ ID NO:33) and is eliminated in form "A" (SEQ ID NO:32); f) V1Jns-tPA-gp143/opt32-A and V1Jns-tPA-gp143/opt32-B, comprising a gp 32 opt sequence (SEQ ID NO:34), and wherein the gp160 proteolytic cleavage site is retained in form "B" (SEQ ID NO:33) and is eliminated in form "A" (SEQ ID NO:32); g) V1Jns-tPA-gp143/SRV-1 3'-UTR, wherein the SRV-1 3' UTR comprises SEQ ID NO:35; h) V1Jns-tPA-gp143/opt C1/opt32A and V1Jns-tPA-gp143/opt C1/opt32B, wherein the optimized codon usage is derived from opt C1 (SEQ ID NO:30), and gp 32 opt (SEQ ID NO:34), and wherein the gp160 proteolytic cleavage site is retained in form "B" (SEQ ID NO:33) and is eliminated in form "A" (SEQ ID NO:32); i) V1Jns-tPA-gp143/opt all-A, V1Jns-tPA-gp143/opt all-B, V1Jns-tPA-gp143/opt all-A (non IIIB strains), and V1Jns-tPA-gp143/opt all-B (non IIIB strains), wherein the gp160 proteolytic cleavage site is retained in form "B" (SEQ ID NO:33) and is eliminated in form "A" (SEQ ID NO:32); and, j) V1Jns-tPA-gp143/opt32-A/glyB, V1Jns-tPA-gp143/opt32-B/glyB, V1Jns-tPA-gp143/opt C1/opt32-A/glyB, V1Jns-tPA-gp143/opt C1/opt32-B/glyB, V1Jns-tPA-gp143/opt all-A/glyB, V1Jns-tPA-gp143/opt all-B/glyB, V1Jns-tPA-gp143/opt all-A/glyB (non IIIB strains), V1Jns-tPA-gp143/opt all-B/glyB (non IIIB strains), which respectively contain gp 32 opt (SEQ ID NO:34) and/or opt C1 (SEQ ID NO:30), wherein the gp160 proteolytic cleavage site is retained in form "B" (SEQ ID NO:33) and is eliminated in form "A" (SEQ ID NO:32), and wherein the five carboxy-terminal amino acids of the expressed protein are NRLIKA (SEQ ID NO:27), and combinations thereof.

2. The polynucleotide of claim 1 which induces anti-**HIV** neutralizing antibody, **HIV** specific T-cell immune responses, or both, wherein said

polynucleotide comprises a gene encoding an **HIV** gag, **HIV** protease and combinations thereof.

3. A method for inducing immune responses in a vertebrate against **HIV** epitopes which comprises introducing between 1 ng and 100 mg of the polynucleotide of claim 1 into the tissue of the vertebrate.

4. A method for using a rev independent **HIV** gene to induce immune responses in vivo which comprises: a) synthesizing the rev independent **HIV** gene; b) linking the synthesized gene to regulatory sequences such that the gene is expressible by virtue of being operatively linked to control sequences which, when introduced into a living tissue, direct the transcription initiation and subsequent translation of the gene.

5. A method for inducing immune responses against infection or disease caused by virulent strains of **HIV** which comprises introducing into the tissue of a vertebrate the polynucleotide of claim 1.

6. A method for inducing anti-**HIV** immune responses in a primate which comprises introducing the polynucleotide of claim 1 into the tissue of the primate and concurrently administering interleukin 12, GM-CSF, or combinations thereof parenterally.

7. A method of inducing an antigen presenting cell to stimulate **cytotoxic** and helper T-cell proliferation and effector functions including lymphokine secretion specific to **HIV** antigens which comprises exposing cells of a vertebrate in vivo to the polynucleotide of claim 1.

8. A method of inducing an immune response to **HIV** which comprises administration of the polynucleotide of claim 1 and administration of an attenuated **HIV**, a killed **HIV**, an **HIV** protein, a fragment of an **HIV** protein, or combinations thereof, wherein the administration of the polynucleotide is prior to or simultaneous with or subsequent to the administration of the attenuated **HIV**, the killed **HIV**, the **HIV** protein, the fragment of the **HIV** protein or the combinations thereof.

9. A method of inducing an immune response to **HIV** which comprises administration of the polynucleotide of claim 1 with an adjuvant.

10. A method of treating **HIV** infection which comprises administration of the polynucleotide of claim 1 to a patient and administration of an anti-**HIV** compound to the patient, wherein the administration of the polynucleotide is prior to or simultaneous with or subsequent to the administration of the anti-**HIV** compound.

11. A method of expressing a peptide in a host comprising administration of the synthetic polynucleotide of claim 1 to the host.

12. A method of increasing production of a recombinant protein by a host, comprising: a) transforming a host cell with the synthetic polynucleotide of claim 1 to produce a transformed host; and b) cultivating the transformed host under conditions that permit expression of the synthetic polynucleotide and production of the recombinant protein.

L27 ANSWER 7 OF 33 USPATFULL on STN
2002:322019 METHOD FOR INDUCING IMMUNITY TO VIRUSES.
KANEKO, YUTARO, TOKYO, JAPAN
KOZBOR, DANUTA, PHILADELPHIA, PA, UNITED STATES
US 2002182180 A1 20021205
APPLICATION: US 1998-87513 A1 19980529 (9) <--
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to methods for inducing cellular immunity

against viruses which undergo mutation by introducing a mutant form of an envelope (env) glycoprotein of the virus with an altered or deleted immunodominant epitope. Also disclosed are **vaccines** and methods of producing the same.

CLM What is claimed is:

1. A method of inducing cellular immunity against a virus comprising administering to a patient a **nucleic acid** encoding an envelope glycoprotein of said virus, in an amount sufficient to induce cellular immunity against the virus, wherein said envelope glycoprotein (a) contains a modified immunodominant epitope; and (b) induces cellular immunity to a conserved epitope of said envelope glycoprotein.

2. The method of claim 1, wherein said **nucleic acid** is introduced into antigen presenting cells (APCs) and said APCs are administered to the patient.

3. The method of claim 1, wherein said virus is a lentivirus.

4. The method of claim 2, wherein said lentivirus is **human immunodeficiency virus** (**HIV**).

5. The method of claim 1, wherein said immunodominant epitope is the third variable loop (V3) of said envelope glycoprotein.

6. The method of claim 1, wherein said immunodominant epitope is a neutralization epitope.

7. The method of claim 2, wherein said APCs stimulate peripheral blood mononuclear cells (PBMCs).

8. The method of claim 7, wherein said PBMCs exhibit increased **cytotoxic** T-lymphocyte (**CTL**) activity against conserved epitopes of the envelope glycoprotein compared to PBMCs stimulated with APCs encoding a full-length envelope glycoprotein.

9. The method of claim 2, wherein said APCs encoding the modified envelope glycoprotein are resistant to antibody-dependent cell-mediated cytotoxicity (ADCC).

10. The method of claim 2, wherein said APCs encoding the modified envelope glycoprotein do not form syncytia.

11. The method of claim 2, wherein said APCs encoding the modified envelope glycoprotein do not undergo apoptosis.

12. The method of claim 2, wherein said APCs encoding the modified envelope glycoprotein induce cellular immunity to said virus without inducing apoptosis of CD4+ T cells.

13. The method of claim 1, wherein the immunodominant epitope is deleted.

14. A method for preparing a **vaccine** against a virus comprising: (a) introducing into a vector **DNA** or liposome a **nucleic acid** encoding an envelope glycoprotein of said virus, wherein said envelope glycoprotein contains a modified immunodominant epitope; and (b) mixing said vector **DNA** or liposome with a suitable adjuvant.

15. The method of claim 14, wherein said **nucleic acid** is introduced into APCs and said APCs are mixed with the adjuvant.

16. The method of claim 14, wherein said virus is a lentivirus.

17. The method of claim 15, wherein said lentivirus is **human immunodeficiency virus** (**HIV**).

18. The method of claim 14, wherein said immunodominant epitope is the third variable loop (V3) of said envelope glycoprotein.

19. A **vaccine** for inducing cellular immunity against a virus comprising: (a) cells expressing on their surfaces an envelope glycoprotein of said virus, wherein said envelope glycoprotein contains a modified immunodominant epitope; and (b) an adjuvant.

20. The method of claim 19, wherein said virus is **human immunodeficiency virus** (**HIV**).

L27 ANSWER 8 OF 33 USPATFULL on STN
2002:251744 CHIMERIC RECEPTOR GENES AND CELLS TRANSFORMED THEREWITH.
ESHHAR, ZELIG A., REHOVOT, ISRAEL
SCHINDLER, DANIEL, REHOVOT, ISRAEL
WAKS, TOVA, PETACH TIKVA, ISRAEL
GROSS, GIDEON, HEVEL KORAZIM, ISRAEL
ROSENBERG, STEVEN A., POTOMAC, MD, UNITED STATES
HWU, PATRICK, ROCKVILLE, MD, UNITED STATES
US 2002137697 A1 20020926
APPLICATION: US 1995-547263 A1 19951024 (8) <--
PRIORITY: IL 1992-101288 19920318
IL 1993-104570 19930131
WO 1993-US2506 19930318
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Chimeric receptor genes suitable for endowing lymphocytes with antibody-type specificity include a first gene segment encoding a single-chain Fv domain of a specific antibody and a second gene segment encoding all or part of the transmembrane and cytoplasmic domains, and optionally the extracellular domain, of an immune cell-triggering molecule. The chimeric receptor gene, when transfected to immune cells, expresses the antibody-recognition site and the immune cell-triggering moiety into one continuous chain. The transformed lymphocytes are useful in therapeutic treatment methods.

CLM What is claimed is:

1. A chimeric gene comprising a first gene segment encoding a single-chain Fv domain (scFv) of a specific antibody and a second gene segment encoding partially or entirely the transmembrane and cytoplasmic, and optionally the extracellular, domains of an immune cell-triggering molecule which, upon transfection to immune cells, expresses the antibody-recognition site and the immune cell-triggering moiety into one continuous chain.

2. A chimeric gene according to claim 1 wherein the second gene segment further comprises partially or entirely the extracellular domain of the immune cell-triggering molecule.

3. A chimeric gene according to claim 1 wherein the first gene segment encodes the scFv domain of an antibody against tumor cells.

4. A chimeric gene according to claim 1 wherein the first gene segment encodes the scFv domain of an antibody against virus infected cells.

5. A chimeric gene according to claim 4 wherein the virus is **HIV**.

6. A chimeric gene according to claim 1 wherein the second gene segment encodes a lymphocyte receptor chain.

7. A chimeric gene according to claim 6 wherein the gene encodes a chain of the T cell receptor.

8. A chimeric gene according to claim 7 encoding a subunit of the T cell receptor.

9. A chimeric gene according to claim 8 comprising a gene segment encoding the α, γ, γ or δ chain of the antigen-specific T cell receptor.

10. A chimeric gene according to claim 1 wherein the second gene segment encodes a polypeptide of the TCR/CD3 complex.

11. A chimeric gene according to claim 10 encoding the zeta or eta isoform chain.

12. A chimeric gene according to claim 1 wherein the second gene segment encodes a subunit of the Fc receptor or IL-2 receptor.

13. A chimeric gene according to claim 12 wherein the second gene segment encodes a common subunit of IgE and IgG binding Fc receptors.

14. A chimeric gene according to claim 13 wherein said subunit is the gamma chain.

15. A chimeric gene according to claim 14 comprising a gene segment coding for the CD16α chain of the FcγRIII or FcγRII.

16. A chimeric gene according to claim 12 comprising a gene segment coding for the α or β subunit of the IL-2 receptor.

17. An expression vector comprising a chimeric gene according to claim 1.

18. An immune cell endowed with antibody specificity transformed with an expression vector according to claim 17.

19. An immune cell endowed with antibody specificity comprising a chimeric gene according to claim 1.

20. An immune cell according to claim 19 selected from the group consisting of a natural killer cell, a lymphokine activated cell, a **cytotoxic** T cell, a helper T cell and a subtype thereof.

21. A primary T cell endowed with antibody specificity transformed with an expression vector according to claim 17.

22. A hematopoietic stem cell endowed with antibody specificity transformed with an expression vector according to claim 17.

23. A tumor infiltrating lymphocyte cell endowed with antibody specificity transformed with an expression vector according to claim 17.

24. A method of treatment of a tumor in a patient comprising transforming lymphocyte cells of the patient with an expression vector comprising a chimeric gene according to claim 1 in which the first gene segment encodes a scFv domain of an antibody directed against the tumor cells, and administering the transformed and thus activated cells to the patient, said cells being targeted to the tumor cells thus causing tumor regression.

25. A method according to claim 24 wherein peripheral blood cells of the patient are transformed.

26. A method according to claim 24 wherein, hematopoietic stem cells of the patient are transformed.

27. A method according to claim 24 wherein primary T cells of the patient are transformed.

28. Chimeric **DNA** sequence encoding a membrane-bound protein, said chimeric **DNA** comprising in reading frame: a **DNA** sequence encoding a

signal sequence which directs the membrane bound protein to the surface membrane; a **DNA** sequence encoding a non-MHC restricted extracellular binding domain of a surface membrane protein which is a single-chain antibody that binds specifically to at least one ligand, wherein said ligand is a protein on the surface of a cell or a viral protein; a transmembrane domain from a protein selected from the group consisting of the CD3 zeta chain, the CD3 gamma chain, the CD3 delta chain and the CD3 epsilon chain; a cytoplasmic signal-transducing domain of a protein that activates an intracellular messenger system selected from the group consisting of the CD3 zeta chain, the CD3 gamma chain, the CD3 delta chain, and the CD3 epsilon chain, wherein said extracellular domain and cytoplasmic domain are not naturally joined together and said cytoplasmic domain is not naturally joined to an extracellular ligand-binding domain, and when said chimeric **DNA** is expressed as a membrane bound protein in a selected host cell under conditions suitable for expression, said membrane bound protein initiates signalling in said host cell.

29. A **DNA** according to claim 28 wherein said extracellular domain is a single-chain antibody, or portion thereof containing ligand binding activity.

30. A **DNA** sequence according to claim 28, wherein said single-chain antibody recognizes an antigen selected from the group consisting of viral antigens and tumor cell associated antigens.

31. A **DNA** sequence according to claim 28, wherein said single-chain antibody is specific for the **HIV** env glycoprotein.

32. A **DNA** sequence according to claim 28 where said cytoplasmic domain is zeta.

33. A **DNA** sequence according to claim 28, wherein said transmembrane domain is naturally joined to said cytoplasmic domain.

34. An expression cassette comprising a transcriptional initiation region, a **DNA** sequence according to claim 28 under the transcriptional control of said transcriptional initiation region, and a transcriptional termination region.

35. An expression cassette according to claim 34, wherein said transcriptional initiation region is functional in a mammalian host.

36. A retroviral RNA or **DNA** construct comprising an expression cassette according to claim 35.

37. A cell comprising a **DNA** sequence according to claim 28.

38. A cell according to claim 37, wherein said cytoplasmic domain is the CD3 zeta chain.

39. A cell according to claim 37, wherein said cell is a mammalian cell.

40. A cell according to claim 37, wherein said mammalian cell is a human cell.

41. A cell according to claim 37, wherein said cell is a hematopoietic stem cell.

L27 ANSWER 9 OF 33 USPATFULL on STN
2002:192074 IMMUNIZATION OF INFANTS.
BOT, ADRIAN, SAN DIEGO, CA, UNITED STATES
BONA, CONSTANTIN, NEW YORK, NY, UNITED STATES
US 2002103145 A1 20020801
APPLICATION: US 1999-308511 A1 19990519 (9) <--

DOCUMENT TYPE: Utility; APPLICATION.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to methods and compositions which may be used to immunize infant mammals against a target antigen, wherein an **immunogenically** effective amount of a nucleic acid encoding a relevant epitope of a desired target antigen is administered to the infant. It is based, at least in part, on the discovery that such genetic immunization of infant mammals could give rise to effective cellular and humoral immune responses against target antigens.

CLM What is claimed is:

1. A method for immunizing an infant mammal against a target antigen, comprising inoculating the mammal with an effective amount of a **nucleic acid** encoding a relevant epitope of the target antigen in a pharmaceutically acceptable carrier, such that a therapeutically effective amount of the relevant epitope is expressed in the infant mammal.

2. The method of claim 1, wherein the target antigen is a viral antigen.

3. The method of claim 1, wherein the target antigen is a bacterial antigen.

4. The method of claim 2, wherein the target antigen is a respiratory syncytial virus antigen.

5. The method of claim 2, wherein the target antigen is a rotavirus antigen.

6. The method of claim 2, herein the target antigen is a measles virus antigen.

7. The method of claim 2, wherein the target antigen is a **human immunodeficiency virus** antigen.

8. The method of claim 2, wherein the target antigen is a hepatitis virus antigen.

9. The method of claim 2, wherein the target antigen is a hepatitis B virus antigen.

10. The method of claim 2, wherein the target antigen is a herpes simplex virus antigen.

11. The method of claim 2, wherein the target antigen is an influenza virus antigen.

12. The method of claim 3, wherein the target antigen is a Streptococcus pneumoniae antigen.

13. The method of claim 3, wherein the target antigen is a Hemophilus influenzae antigen.

14. The method of claim 3, wherein the target antigen is a Neisseria meningitidis antigen.

15. The method of claim 3, wherein the target antigen is a Staphylococcus aureus antigen.

16. The method of claim 1, wherein the target antigen is a protozoan antigen.

17. The method of claim 16, wherein the target antigen is a malaria antigen.

18. A method for inducing a **cytotoxic** T cell response to a target

antigen in an infant mammal, comprising inoculating the mammal with an effective amount of a **nucleic acid** encoding a relevant epitope of the target antigen in a pharmaceutically acceptable carrier, such that a therapeutically effective amount of the relevant epitope is expressed in the infant mammal.

19. The method of claim 19, wherein the infant mammal carries a detectable amount of maternal antibodies

20. A method for immunizing an infant mammal against a pathogen comprising inoculating the mammal with an effective amount of **nucleic acid** encoding more than one relevant epitope of one or more target antigen associated with the pathogen in a pharmaceutically acceptable carrier, such that therapeutically effective amounts of the relevant epitopes are expressed in the infant mammal.

21. The method of claim 20, wherein the relevant epitopes are encoded by the same **nucleic acid** molecule.

22. The method of claim 20, wherein the relevant epitopes are encoded by different **nucleic acid** molecules.

23. The method of claim 20, wherein the pathogen is an influenza virus.

24. A method for inducing a **cytotoxic** T cell response against a pathogen in an infant mammal, comprising inoculating the mammal with an effective amount of **nucleic acid** encoding more than one relevant epitope of one or more target antigen associated with the pathogen in a pharmaceutically acceptable carrier, such that therapeutically effective amounts of the relevant epitopes are expressed in the infant mammal

25. The method of claim 24, wherein the target antigen is a viral antigen.

26. The method of claim 24, wherein the target antigen is a bacterial antigen.

27. The method of claim 25, wherein the target antigen is a respiratory, syncytial virus antigen.

28. The method of claim 25, wherein the target antigen is a rotavirus antigen.

29. The method of claim 25, wherein the target antigen is a measles virus antigen.

30. The method of claim 25, wherein the target antigen is a **human immunodeficiency virus** antigen.

31. The method of claim 25, wherein the target antigen is a hepatitis virus antigen.

32. The method of claim 31, wherein the target antigen is a hepatitis B virus antigen.

33. The method of claim 25, wherein the target antigen is a herpes simplex virus antigen.

34. The method of claim 25, wherein the target antigen is an influenza virus antigen.

35. The method of claim 26, wherein the target antigen is a Streptococcus pneumoniae antigen.

36. The method of claim 26, wherein the target antigen is a Hemophilus influenzae antigen.

37. The method of claim 26, wherein the target antigen is a Neisseria meningitidis antigen.

38. The method of claim 26, wherein the target antigen is a Staphlyococcus aureus antigen.

39. The method of claim 24, wherein the target antigen is a protozoan antigen.

40. The method of claim 39, wherein the target antigen is a malaria antigen.

41. A composition of **nucleic acid** encoding one or more relevant epitopes of one or more target antigens, for use in the preparation of a **vaccine** for use in an infant mammal.

42. A composition of **nucleic acid** encoding one or more relevant epitopes of one or more target antigens, for use in the preparation of an **immunogenic** composition which may be used in a method of inducing a cellular immune response in an infant mammal.

43. A method for immunizing an infant mammal having an immune response which has susceptibility to high-zone tolerance against a target antigen, comprising inoculating the mammal with an effective amount of a **nucleic acid** encoding a relevant epitope of the target antigen in a pharmaceutically acceptable carrier, such that a therapeutically effective amount of the relevant epitope is expressed in the infant mammal.

44. A method for immunizing an infant mammal having an immune response which has a humoral response of reduced magnitude and restricted isotype, comprising inoculating the mammal with an effective amount of a **nucleic acid** encoding a relevant epitope of the target antigen in a pharmaceutically acceptable carrier, such that a therapeutically effective amount of the relevant epitope is expressed in the infant mammal.

45. A method for immunizing an infant mammal having an immune response which has a Th2 biased helper response, comprising inoculating the mammal with an effective amount of a **nucleic acid** encoding a relevant epitope of the target antigen in a pharmaceutically acceptable carrier, such that a therapeutically effective amount of the relevant epitope is expressed in the infant mammal.

46. A method for immunizing an infant mammal having an immune response which has a cellular immune response of reduced magnitude, comprising inoculating the mammal with an effective amount of a **nucleic acid** encoding a relevant epitope of the target antigen in a pharmaceutically acceptable carrier, such that a therapeutically effective amount of the relevant epitope is expressed in the infant mammal.

47. A method of increasing the level of maternal antibodies to a target antigen in an infant mammal, comprising immunizing the pregnant mother with an effective amount of a **nucleic acid** encoding a relevant epitope of the target antigen in a pharmaceutically acceptable carrier, such that a therapeutically effective amount of the relevant epitope is expressed in the infant mammal.

L27 ANSWER 10 OF 33 USPATFULL on STN
2002:171615 IMMUNOTHERAPY USING **CYTOTOXIC** T LYMPHOCYTES (**CTL**).
STAUSS, HANS JOSEF, LONDON, UNITED KINGDOM
US 2002090362 A1 20020711
APPLICATION: US 1998-101413 A1 19980807 (9) <--
WO 1997-GB118 19970117

PRIORITY: GB 1996 870 19960117
GB 1996-23471 19961112
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method of treating a patient with a disease wherein the patient contains diseased cells which cells contain, or are associated with, an abnormal molecule or an abnormally elevated amount of a molecule and which cells are capable of presenting at least part of said molecule on their surface by an HLA class I (or equivalent) molecule, the method comprising administering to the patient a therapeutically effective amount of **cytotoxic** T lymphocytes (**CTL**) which recognize at least part of said molecule when presented by an HLA class I (or equivalent) molecule on the surface of a cell characterized in that the **cytotoxic** T lymphocytes are not derived from the patient with a disease. Preferably, the **CTL** are derived from an individual which individual does not carry the HLA class I (or equivalent) molecule type which, in the patient, presents at least part of said abnormal molecule, or molecule abnormally elevated, contained in or associated with the disease cells of said patient.

CLM What is claimed is:

1. A method of treating a patient with a disease wherein the patient contais diseased cells which cells contain, or are associated with, an abnormal molecule or an abnormally elevated amount of a molecule and which cells are capable of presenting at least part of said molecule on their surface by an HLA class I (or equivalent) molcule, the method comprising administering to the patient a therapeutically effective amount of **cytotoxic** T lymphocytes (**CTL**) which recongnise at least part of said molecule when presented by an HLA class I (or equivalent) molecule on the sarface of a cell characterised in that the **cytotoxic** T lymphocytes are not derived from the patient with a disease.

2. A method according to claim 1 wherein the **CTL** are a clonal population of **CTL**.

3. A method according to claim 1 or 2 wherein the **CTL** are substantially free of other cell types.

4. A method according to any one of claims 1 to 3 wherein said molecule is a polypeptide.

5. A method accordiag to any one of claims 1 to 4 wherein the **CTL** are derived from an individual other than the patient.

6. A method according to any one of claims 1 to 5 wherein the **CTL** are derived from an individual which individual does not carry the HLA class I (or equivalent) molecule type which, in the patient, presents at least part of said abnormal molecule, or molecule abnormally elevated, contained in or associated with the diseased cells of said patient.

7. A method according to claim 4 wherein said polypeptide is a mutant polypeptide associated with said diseased cells.

8. A method according to claim 4 wherein said polypeptide is present at a higher level in said diseased cells compared to non-diseased cells.

9. A method according to any one of the preceding claims wherein the disease is a cancer.

10. A method according to claim 9 wherein the cancer is any one of any one of breast cancer; bladder cancer; lung cancer; prostate cancer; thyroid cancer; leukaemias and lymphomas such as CML, ALL, AML, PML; colon cancer; glioma; seminoma; liver cancer; pancreatic cancer; bladder cancer; renal cancer; cervical cancer; testicular cancer; head and neck cancer; ovarian cancer; neuroblastoma and melanoma.

11. A method according to any one of claims 1 to 8 wherein the disease

is caused by a chronic viral infection.

12. A method according to claim 11 wherein the virus is any one of **HIV**, papilloma virus, Epstein-Barr virus, HTLV-1, hepatitis B virus, hepatitis C virus and herpes virus.

13. A method according to claim 12 wherein the virus is **HIV**

14. A method according to any one of claims 1 to 8 wherein the disease is associated with an abnormally elevated amount of a hormone.

15. A method according to any one of claims 1 to 8 wherein the disease is a bacterial disease caused by a chronic bacterial infection.

16. A method according to any one of the preceding claims further comprising the step of determining the HLA class I (or equivalent) molecule type of the patient prior to administration of the **CTL**.

17. A method according to claim 16 wherein the said type is determined using **DNA** typing.

18. A method according to any one of the preceding claims wherein the patient is human.

19. A method according to claim 16 when dependent on claim 6 wherein said **cytotoxic** T lymphocyte is selected from a library of **CTL** clones, said library comprising a plurality of **CTL** clones derived from individuals with differing HLA class I (or equivalent) molecule type and each said **CTL** clone recognises said diseased cells.

20. A method according to claim 19 wherein each said **CTL** clone recognises at least part of the same molecule contained in or associated with said diseased cells.

21. Use of **cytotoxic** T lymphocytes in the manufacture of a medicament for treating a patient with a disease wherein the patient contains diseased cells which cells contain, or are associated with, an abnormal molecule or an abnormally elevated amount of a molecule and are capable of presenting at least part of said molecule on their surface by an HLA class I (or equivalent) molecule, wherein the **cytotoxic** T lymphocytes recognise at least part of said molecule when presented by an HLA class I (or equivalent) molecule on the surface of a cell and they are not derived from the patient with the a disease.

22. A method of making a clonal population of **cytotoxic** T lymphocytes (**CTL**) reactive against a selected molecule the method comprising the step of (a) co-culturing a sample containing **CTL** or a precursor, thereof derived from a healthy individual with a stimulator cell which expresses HLA class I (or equivalent) molecules on its surface and that presents at least a part of the selected molecule in a large proportion of occupied said HLA class I (or equivalent) molecules present on the surface of said stimulator cell and (b) selecting a **CTL** clone reactive against said selected molecule when at least a part of said molecule is presented by an HLA class I (or equivalent) molecule on the surface of a cell.

23. A method according to claim 22 wherein the healthy individual does not carry the HLA class I (or equivalent) molecule type which on the stimulator cell, presents at least a part of the selected molecule.

24. A method according to claim 22 or 23 wherein said sample containing **CTL** or a precursor thereof is PBMC.

25. A method according to any one of claims 22 to 24 wherein said molecule is a polypeptide.

26. A method according to any one of claims 22 to 25 wherein said selected molecule is an abnormal molecule associated with a diseased cell, or a molecule associated with a diseased cell wherein an abnormally elevated amount of said molecule is present in said diseased cell.

27. A method according to claim 26 wherein the said selected molecule is a mutant polypeptide associated with a diseased cell or a polypeptide present at a higher level in said diseased cell compound to a non-diseased cell.

28. A method according to claim 26 or 27 wherein said diseased cell is any one of a cancer cell, a virus-infected cell, a bacterium infected cell and a cell expressing an abnormally elevated amount of a hormone.

29. A method according to any one of claims 22 to 28 wherein the healthy individual is a human.

30. A method according to claim 29 wherein the said selected molecule is any one of cyclin D1, cyclin E, mdm 2, EGF-R, erb-B2, erb-B3, FGF-R, insulin-like growth factor receptor, Met, myc, p53, BCL-2, ie mutant Ras, mutant p53 a polypeptide associated with the BCR/ABL translocation in CML and ALL; mutant CSF-1 receptor, mutant APC, mutant RET, mutant EGFR, a polypeptide associated with PML/RARA translocation in PML, a polypeptide associated with E2A-PBX1 translocation in pre B leukaemias and in childhood acute leukaemias, human papilloma virus proteins, Epstein-Barr virus proteins, HTLV-1 proteins, hepatitis B or C virus proteins, herpes-like virus proteins and **HIV** encoded proteins.

31. A method according to any one of claims 22 to 30 further comprising determining the HLA class I (or equivalent) type of the healthy individual.

32. A method according to claim 31 wherein said HLA class I (or equivalent) type is determined by **DNA** analysis.

33. A method according to any one of claims 20 to 32 wherein said stimulator cell has a type of HLA class I (or equivalent) molecule on its surface which HLA class I (or equivalent) molecule type is not present in the healthy individual.

34. A method according to any one of claims 22 to 33 wherein said stimulator cell is a cell which is substantially incapable of loading said HLA class I (or equivalent) molecule with at least a part of said selected molecule.

35. A method according to claim 34 wherein said cell is a mammalian cell defective in the expression of a peptide transporter.

36. A method according to claim 35 wherein the mammalian cell lacks or has a reduced level of the TAP peptide transporter.

37. A method according to claim 34 wherein said cell is an insect cell.

38. A method according to claim 37 wherein said cell is a Drosophila cell.

39. A method according to any one of claims 22 to 38 wherein the stimulator cell is a host cell transfected with a **nucleic acid** molecule capable of expressing said HLA class I (or equivalent) molecule.

40. A method according to claim 39 wherein said host cell before transfection expresses substantially no HLA class I (or equivalent) molecules.

41. A method according to any one of claims 22 to 40 wherein said stimulator cell expresses a molecule important for T cell costimulation.

42. A method according to claim 41 wherein the molecule important for T cell costimulation is any of B7.1, B7.2, ICAM-1 and LFA3.

43. A method according to any one of claims 22 to 42 wherein substantially all said HLA class I (or equivalent) molecules expressed on the surface of said stimulator cell are of the same type.

44. A clonal population of **cytotoxic** T lymphocytes reactive against a selected molecule obtainable by the method of any one of claims 22 to 43.

45. A clonal population of **cytotoxic** T lymphocytes reactive against a selected molecule wherein the said **CTL** has a high avidity for a cell presenting said selected molecule in a HLA class I (or equivalent) molecule.

46. A clonal population of **cytotoxic** T lymphocytes according to claim 44 or 45 for use in medicine.

47. A pharmaceutical composition comprising a clonal population of **cytotoxic** T lymphocytes reactive against a selected molecule according to claim 44 or 45 and a pharmaceutically acceptable carrier.

48. Use of a clonal population of **cytotoxic** T lymphocytes derived from a healthy individual and reactive against a selected abnormal molecule derived from a diseased cell from a patient with a disease, or a selected molecule derived from a diseased cell from a patient with a disease wherein an abnormally elevated amount of said molecule is present in said diseased cell, in the manufacture of a medicament for treating a patient with the disease wherein said healthy individual has a different HLA type to said patient.

49. A library of **CTL** clones, said library comprising a plurality of **CTL** clones derived from individuals and each said **CTL** clone is restricted by a different HLA class I allele and recognises a molecule associated with a selected disease.

50. A therapeutic system comprising (a) means to determine the HLA class I (or equivalent) type of a patient to be treated and (b) a library of **CTL** clones as defined in claim 49.

51. A method of making a **cytotoxic** T lymphocyte (**CTL**) suitable for treating a patient, the method comprising making a clonal population of **CTL** by the method of any one of claims 22 to 43; preparing a genetic construct capable of expressing the T-cell receptor (TCR) of the said clonal population of **CTL**, or a functionally equivalent molecule; and introducing said genetic construct into a **CTL** or precursor thereof which **CTL** or precursor is derived from said patient.

52. A **cytotoxic** T lymphocyte suitable for treating a patient obtainable by the method of claim 51.

53. A method of treating a patient with a disease wherein the patient contains diseased cells which cells contain, or are associated with, an abnormal molecule or an abnormally elevated amount of a molecule and which cells are capable of presenting at least part of said molecule on their surface by an HLA class I (or equivalent) molecule, the method comprising administering to the patient a therapeutically effective amount of **cytotoxic** T lymphocytes (**CTL**) which recognise at least part of said molecule when presented by an HLA class I (or equivalent) molecule on the surface of a cell wherein the **CTL** is a **CTL** according to claim 52.

54. Use of **cytotoxic** T lymphocytes in the manufacture of a medicament for treating a patient with a disease wherein the patient contains diseased cells which cells contain, or are associated with, an abnormal molecule or an abnormally elevated amount of a molecule and are capable of presenting at least part of said molecule on their surface by an HLA class I (or equivalent) molecule, wherein the **cytotoxic** T lymphocytes recognise at least part of said molecule when presented by an HLA class I (or equivalent) molecule on the surface of a cell and wherein the **CTL** is a **CTL** according to claim 52.

55. Any novel method of treatment using **cytotoxic** T lymphocytes as herein disclosed.

L27 ANSWER 11 OF 33 USPATFULL on STN
2002:157619 NON-**IMMUNOGENIC** PRODRUGS AND SELECTABLE MARKERS FOR USE IN GENE THERAPY.
JOLLY, DOUGLAS J., LEUCADIA, CA, UNITED STATES
MOORE, MARGARET D., SAN DIEGO, CA, UNITED STATES
CHADA, SUNIL, VISTA, CA, UNITED STATES
US 2002082224 A1 20020627
APPLICATION: US 1998-6298 A1 19980113 (9) <--
PRIORITY: US 1997-35473P 19970114 (60)
US 1997-38339P 19970227 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides methods for delivering a gene delivery vehicle to a warm-blooded animal, comprising the step of administering to a warm-blooded animal a gene delivery vehicle which directs the expression of a non-**immunogenic** selectable marker. Within other aspects, methods are provided for delivering a gene delivery vehicle to a warm-blooded animal, comprising the step of administering to a warm-blooded animal a gene delivery vehicle which directs the expression of a non-**immunogenic** molecule which is capable of activating an otherwise inactive compound into an active compound.

CLM What is claimed is:
1. A method of delivering a gene delivery vehicle to a warm-blooded animal, comprising administering to a warm-blooded animal a gene delivery vehicle which directs the expression of a non-**immunogenic** selectable marker.

2. A method of delivering a gene delivery vehicle to a warm-blooded animal, comprising administering to a warm-blooded animal a gene delivery vehicle which directs the expression of a non-**immunogenic** molecule which is capable of activating an otherwise inactive compound into an active compound.

3. The method according to claims 1 or 2 wherein said vector construct also directs the expression of a selected heterologous **nucleic acid** seqeunce.

4. The method according to claim 1 wherin said selectable marker is selected from the group consisting of alkaline phosphatase, α-Galactosidase, β-glucosidase, β-glucuronidase, Carboxypeptidase A, Cytochrome P450, γ-glutamyl transferase; reductases such as Azoreductase, DT diaphorase and Nitroreductase; and oxidases such as glucose oxidase and xanthine oxidase.

5. The method according to claim 1 wherin said compound capable of activating an otherwise inactive compound into an active compound is selected from the group consisting of alkaline phosphatase, α-Galactosidase, β-glucosidase, β-glucuronidase, Carboxypeptidase A, Cytochrome P450, γ-glutamyl transferase; reductases such as Azoreductase, DT diaphorase and Nitroreductase; and oxidases such as glucose oxidase and xanthine oxidase.

6. The method according to any one of claim 1 or 2 wherein said gene delivery vehicle is a retroviral vector construct.

7. The method according to any one of claim 1 or 2 wherein said gene delivery vehicle is selected from the group consisting of poliovirus vectors, rhinovirus vectors, pox virus vectors, canary pox virus vectors, **vaccinia** virus vectors, influenza virus vectors, adenovirus vectors, parvovirus vectors, adeno-associated viral vectors, herpesvirus vectors, SV 40 vectors, lenti virus vectors, measles virus vectors, astrovirus vectors, corona virus vectors and Alphavirus vectors.

8. The method according to any one of claim 1 or 2 wherein said gene delivery vehicle is selected from the group consisting of polycation condensed nucleic acids, liposome entrapped nucleic acids, naked **DNA** or RNA and producer cell lines.

9. The method according to claim 3 wherein said heterologous sequence is a gene encoding a **cytotoxic** protein.

10. The method according to claim 9 wherein said **cytotoxic** protein is selected from the group consisting of ricin, abrin, diphtheria toxin, cholera toxin, gelonin, pokeweed, antiviral protein, tritin, Shigella toxin and Pseudomonas exotoxin A.

11. The method according to claim 3 wherein said heterologous sequence is an antisense sequence.

12. The method according to claim 3 wherein said heterologous sequence encodes an immune accessory molecule.

13. The method according to claim 12 wherein said immune accessory molecule is selected from the group consisting of α interferon, βinterferon, IL-1, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11I and IL-13.

14. The method according to claim 12 wherein said immune accessory molecule is selected from the group consisting of IL-2, IL-12 and gamma-interferon.

15. The method according to claim 12 wherein said immune accessory molecule is selected from the group consisting of ICAM-1, ICAM-2, β-microglobin, LFA3, and HLA class I and HLA class II molecules.

16. The method according to claim 3 wherein said heterologous sequence is a ribozyme.

17. The method according to claim 3 wherein said heterologous sequence is a replacement gene.

18. The method according to claim 17 wherein said replacement gene encodes a protein selected from the group consisting of Factor VIII, ADA, HPRT, CFTCR and the LDL Receptor.

19. The method according to claim 3 wherein said heterologous sequence encodes an **immunogenic** portion of a virus selected from the group consisting of HBV, HCV, HPV, EBV, FeLV, FIV and **HIV**.

20. The method according to claims 1 or 2 wherein said gene delivery vehicle is introduced into cells ex vivo, followed by administration of said gene delivery vehicle containing cells to said warm-blooded animal.

L27 ANSWER 12 OF 33 USPATFULL on STN
2002:102297 Self-enhancing, pharmacologically controllable expression systems.
Mueller, Rolf, Marburg, GERMANY, FEDERAL REPUBLIC OF
Sedlacek, Hans-Harald, Marburg, GERMANY, FEDERAL REPUBLIC OF

Aventis Pharma Deutschland GmbH, Frankfurt, GERMANY, FEDERAL REPUBLIC OF
(non-U.S. corporation)
US 6383785 B1 20020507
APPLICATION: US 1997-987348 19971209 (8) <--
PRIORITY: DE 1996-19651443 19961211
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention relates to a nucleic acid construct which constitutes a self-enhancing expression system and which comprises the following components:

at least one first structural gene that encodes an active compound;

at least one second structural gene that encodes a transcription factor protein; and

at least one activation sequence comprised of at least one sequence that binds the transcription factor protein and at least one promoter sequence;

wherein each activation sequence activates the expression of a structural gene and the expression of the transcription factor protein; and to the use of the nucleic acid construct for preparing a drug for treating diseases.

CLM What is claimed is:

1. A **nucleic acid** construct that comprises: in a 5' to 3' direction, at least one structural gene; and at least one gene that encodes a transcription factor protein, wherein said structural gene and said gene that encodes a transcription factor protein are mutually linked by an internal ribosome entry site (IRES) sequence; and at least one activation sequence comprised of at least one sequence that binds the transcription factor protein and at least one promoter sequence, wherein the binding of said transcription factor protein to said activation sequence activates the expression of said structural gene and the expression of said gene that encodes a transcription factor protein.

2. A **nucleic acid** construct according to claim 1, further comprising: a nuclear export signal sequence appended to the first structural gene; a third promoter; and a nuclear export factor gene sequence.

3. A **nucleic acid** construct according to claim 1, comprising two structural genes that encode transcription factors, the two structural genes being mutually linked by an IRES sequence or by an activation sequence.

4. A **nucleic acid** construct according to claim 3, wherein said transcription factor protein genes are non-identical and transcription factor proteins produced from said genes binds said transcription factor protein binding sequences in the **nucleic acid** construct.

5. A **nucleic acid** construct according to claim 1, wherein said activation sequence comprises a sequence for binding a transcription factor protein, the sequence selected from the group consisting of the GAL4-protein gene, the LexA-protein gene, the Lac-repressor protein gene, the tetracyclin repressor protein gene, and the ZFHD-1 protein gene; a promoter sequence selected from the group consisting of the basal c-fos promoter in combination with the HSV-1 VP16 transactivation domain, the U2 sn RNA promoter in combination with a sequence of the Oct-2 activation domain, and the HSV TK promoter; and a transcription factor protein gene selected from the group consisting of the **DNA**-binding domain of the GAL4-protein gene, the **DNA**-binding domain of LexA-protein gene, the LacI-repressor protein gene, the tetracyclin repressor protein gene, and the ZFHD-1 protein gene.

6. A **nucleic acid** construct according to claim 5, wherein said

transcription factor protein gene comprises a portion that codes for the SV40 nuclear localization signal and the HSV-1 VP 16 acid transactivation domain.

7. A **nucleic acid** construct according to claim 1, wherein at least one promoter is selected from the group consisting of RNA polymerase III, RNA polymerase II, CMV promoter and enhancer, SV40 promoter, an HBV promoter, an HCV promoter, an HSV promoter, an HPV promoter, an EBV promoter, an HTLV promoter, an **HIV** promoter, and cdc25C promoter, a cyclin a promoter, a cdc2 promoter, a bmyb promoter, a DHFR promoter and an E2F-1 promoter.

8. A **nucleic acid** construct according to claim 2, wherein the nuclear export signal and the corresponding nuclear export factor are selected from a rev-responsive element/rev protein of a retrovirus selected from the group consisting of **HIV**-1, **HIV**-2, HTLV-1 and HBV.

9. A **nucleic acid** construct according to claim 1, wherein the structural gene encodes a compound selected from the group consisting of inhibitors of cell proliferation, cytostatic or **cytotoxic** proteins, enzymes for cleaving prodrugs, antibodies, fusion proteins between antibody fragments and other proteins, cytokines, growth factors, hormones, receptors for cytokines and growth factors, cytokine antagonists, inflammation inducers, coagulation-inducing factors, coagulation inhibitors, fibrinolysis-inducing proteins, angiogenesis inhibitors, angiogenesis factors, hypotensive peptides, blood plasma proteins, insulin receptor, LDL receptor, enzymes whose absence leads to metabolic diseases or immunosuppression, viral antigens, bacterial antigens, parasitic antigens or tumour antigens, an antiidiotype antibody directed against any of the foregoing for these antigens, and a fusion protein derived from any combination of these.

10. A vector comprising the **nucleic acid** construct of claim 1.

11. A cell which comprises a **nucleic acid** construct as described in claim 1.

12. A process for preparing a **nucleic acid** construct as described in claim 1, comprising: linking a sequence that binds a transcription factor protein to a promoter sequence to form an activation sequence; and linking the activation sequence to at least one structural gene and to at least one gene that encodes a transcription factor protein.

L27 ANSWER 13 OF 33 USPATFULL on STN

2002:95770 Nucleic acid construct for the cell cycle regulated expression of structural genes.

Muller, Rolf, Marburg, GERMANY, FEDERAL REPUBLIC OF
Liu, Ningshu, Marburg, GERMANY, FEDERAL REPUBLIC OF
Zwicker, Jork, Marburg, GERMANY, FEDERAL REPUBLIC OF
Sedlacek, Hans-Harald, Marburg, GERMANY, FEDERAL REPUBLIC OF
Aventis Pharma Deutschland GmbH, Frankfurt, GERMANY, FEDERAL REPUBLIC OF (non-U.S. corporation)

US 6380170 B1 20020430
APPLICATION: US 1998-25343 19980218 (9) <--
PRIORITY: EP 1997-102547 19970218
DOCUMENT TYPE: Utility; GRANTED.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention refers to a nucleic acid construct comprising at least one activator sequence, at least one chimeric promoter module comprising a nucleotide sequence which binds a protein of the E2F family and a protein of the CDF-1 family, and at least one gene, wherein said chimeric promoter module promotes expression of the gene in the cell cycle later than the B-myb promoter but earlier than the cdc25C promoter. The invention also concerns the purification and identification of CDF-1 protein, and use of this protein to develop new

control systems.

CLM What is claimed is:

1. A **nucleic acid** construct comprising: (a) at least one activator sequence; (b) at least one chimeric promoter module comprising a nucleotide sequence selected from the group consisiting of (SEQ ID NO: 1) ACTTGGCGGGAGATTTGAAT and (SEQ ID NO: 2) GCTTGGCGGGAGGTTTGAAT which binds a protein of the E2F family and binds a CDF-1 protein, wherein said activator sequence is upstream of said chimeric promoter module; and (c) at least one gene, wherein said chimeric promoter module promotes expression of said gene occurring later in a cell cycle than the regulation by a B-myb promoter but earlier than regulation by a cdc25C promoter.

2. The **nucleic acid** construct as claimed in claim 1, wherein said activator sequence is upstream of said chimeric promoter module.

3. The **nucleic acid** construct as claimed in claim 1, wherein said chimeric promoter module and said activator sequence cooperatively activate expression of said gene.

4. The **nucleic acid** construct as claimed in claim 1, wherein said activator sequence is cell-specific, metabolic-specific or virus-specific.

5. The **nucleic acid** construct as claimed in claim 4, wherein said cell-specific activator sequence is activated in a cell selected from the group consisting of an endothelial cell, a serosal cell, a smooth muscle cell, a muscle cell, a synovial cell, a macrophage, a lymphocyte, a leukemia cell, a tumor cell, a keratinocyte and a glial cell.

6. The **nucleic acid** construct as claimed in claim 4, wherein said virus-specific activator sequence is a promoter or enhancer sequence derived from a virus selected from the group consisting of HBV, HCV, HSV, HPV, EBV, HTLV, CMV, SV40 and **HIV**.

7. The **nucleic acid** construct as claimed in claim 1, wherein said gene encodes an enzyme or a fusion protein between a ligand and an enzyme which converts or cleaves a precursor of a pharmaceutically active molecule to produce said molecule.

8. The **nucleic acid** construct as claimed in claim 7, wherein said ligand is selected from the group consisting of a growth factor, a cytokine and an antibody protein.

9. The **nucleic acid** construct as claimed in claim 1, wherein said gene encodes a molecule which is selected from the group consisting of a cytokine, a growth factor, a cytokine receptor, a growth factor receptor, a protein having an antiproliferative effect, a protein having an apoptotic effect, a protein having a cytostatic effect, a protein having a **cytotoxic** effect, a protein having an inflammatory effect, a protein having an antiinflammatory effect, a protein having an immunosuppressive effect, an antibody, an antibody fragment, an angiogenesis inhibitor, a coagulation factor, a fibrinolytic compound, an anticoagulant, a blood protein, a viral antigen, a bacterial antigen, a tumor antigen, and a fusion protein between a ligand and one of the afore mentioned substances.

10. The **nucleic acid** construct as claimed in claim 1, which is **DNA**.

11. The **nucleic acid** construct as claimed in claim 1, comprising, in serial arrangement in a 5'-3' orientation: (a) nucleotides of the promoter/early enhancer region of SV40; (b) the sequence (SEQ ID NO: 1) ACCTTGGCGGGAGATT; (c) nucleotides encoding a signal peptide of an immunoglobulin gene; and (d) nucleotides of the cDNA encoding β-glucuronidase.

12. A vector comprising the **nucleic acid** construct as claimed in claim 1.

13. A viral vector comprising the **nucleic acid** construct as claimed in claim 1.

14. A cell comprising at least one **nucleic acid** construct as claimed in claim 1.

15. A pharmaceutical composition comprising the **nucleic acid** of claim 1 and a pharmaceutically acceptable carrier, wherein at least one gene of said **nucleic acid** construct encodes an anti-tumor polypeptide.

16. A process for the preparation of a three-part **nucleic acid** construct, said **nucleic acid** construct comprising: (a) at least one activator sequence; (b) at least one chimeric promoter module comprising a nucleotide sequence selected from the group consisting of (SEQ ID NO: 1) ACTTGGCGGGAGATTTGAAT and (SEQ ID NO: 2) GCTTGGCGGGAGGTTTGAAT which binds a protein of the E2F family and binds a CDF-1 protein, wherein said activator sequence is upstream of said chimeric promoter module; and (c) at least one gene, wherein said chimeric promoter module promotes expression of said gene occurring later in a cell cycle than the regulation by a B-myb promoter but earlier than regulation by a cdc25C promoter; said process comprising ligating parts (a), (b) and (c) together.

L27 ANSWER 14 OF 33 USPATFULL on STN
2001:208643 Induction of REV and TAT specific **cytotoxic** T-cells for **prevention** and treatment of **human immunodeficiency virus** (**HIV**) infection
.

Van Baalen, Carel A., Zeewolde, Netherlands
Osterhaus, Albertus D.M.E., Bunnik, Netherlands
Erasmus Universiteit Rotterdam, Rotterdam, Netherlands (non-U.S. corporation)
US 6319666 B1 20011120
WO 9817309 19980430
APPLICATION: US 1999-284651 19990617 (9) <--
WO 1997-IB1402 19971017 19990617 PCT 371 date 19990617 PCT 102(e) date
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The presence of **cytotoxic** T-cells to the Rev and/or Tat protein in samples from a subject infected with immunodeficiency virus, particularly **HIV** in humans, is an indication of a stable disease condition and a favorable prognosis of lack of progression to disease. **Immunogenic** compositions containing at least one **cytotoxic** T-cell epitope of the Rev and/or Tat protein of an immunodeficiency virus, particularly **HIV**, or a vector encoding the T-cell epitope, may be used to **prevent** infection by disease caused by the immunodeficiency virus, by stimulating, in the host, a specific **cytotoxic** T-cell response specific for the respective Rev and/or Tat proteins.

CLM What is claimed is:

1. A method of treatment of a host, which comprises: stimulating in the host a specific **cytotoxic** T-cell response which is specific for the Rev and/or Tat proteins of the immunodeficiency virus.

2. The method of claim 1 wherein the host is a human host and said immunodeficiency virus is **human immunodeficiency virus**.

3. The method of claim 2 wherein said **cytotoxic** T-cell response is stimulated by administering to the host at least one T-cell epitope selected from the Rev and Tat protein of **HIV** or a vector encoding the at least one **cytotoxic** T-cell epitope.

4. A method of treatment of a host, which comprises: selectively stimulating a **protective** Rev and/or Tat protein-specific **cytotoxic**

T-cell response in said host.

5. The method of claim 4 wherein said immunodeficiency virus is **human immunodeficiency virus** and said host is a human host.

6. The method of claim 5 wherein said selective stimulation is effected by administering to the host at least one T-cell epitope selected from the Rev and Tat proteins of **HIV**.

7. The method of claim 6 wherein said at least one T-cell epitope is administered by administering the Rev and/or Tat **HIV** protein or a homolog thereof in which amino acids have been deleted, inserted or substituted without essentially detracting from the immunological properties thereof with a pharmaceutically-acceptable carrier therefor.

8. The method of claim 6 wherein said at least one T-cell epitope is administered by administering a synthetic peptide having an amino acid sequence corresponding to the T-cell epitope or a homolog thereof in which amino acids have been deleted, inserted or substituted without essentially detracting from the immunological properties thereof with a pharmaceutically-acceptable carrier therefor.

9. The method of claim 5 wherein said selective stimulation is effected by administering to the host a vector encoding at least one **cytotoxic** T-cell epitope selected from the Rev and Tat protein of **HIV**.

10. The method of claim 9 wherein said vector comprises a recombinant vector which expresses the Rev and/or Tat protein of **HIV** or a homolog thereof in which amino acids have been deleted, inserted or substituted without deviating from the immunological properties thereof.

11. At least one **cytotoxic** T-cell epitope selected from the Rev and Tat proteins of **HIV** or a vector encoding the at least one **cytotoxic** T-cell epitope when used as a medicament.

12. The T-cell epitope of claim 11 which is provided by the Rev and/or Tat protein of **HIV** or a homology thereof in which amino acids have been deleted, inserted or substituted without essentially detracting from the immunological properties thereof, in combination with a pharmaceutically-acceptable carrier.

13. The T-cell epitope of claim 11 which is provided by a recombinant vector or a **nucleic acid** molecule which expresses the Rev and/or Tat protein of **HIV**, or a homolog thereof in which amino acids have been deleted, inserted or substituted without essentially detracting from the immunological properties thereof.

14. The T-cell epitope of claim 11 which is provided by a synthetic peptide having an amino acid sequence corresponding to the T-cell epitope, or a homolog thereof in which amino acids have been deleted, inserted or substituted without essentially detracting from the immunological properties thereof, in combination with a pharmaceutical carrier therefor.

L27 ANSWER 15 OF 33 USPATFULL on STN
2001:208480 Detection and treatment of infections with immunoconjugates.
Goldenberg, M. David, Short Hills, NJ, United States
Immunomedics, Inc., Morris Plains, NJ, United States (U.S. corporation)
US 6319500 B1 20011120
APPLICATION: US 1993-158782 19931201 (8) <--
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method of targeting a diagnostic or therapeutic agent to a focus of infection comprises injecting a patient infected with a pathogen parenterally with an antibody conjugate which specifically binds to an

accessible epitope of the pathogen or of a pathogen associated antigen accreted at the focus of infection, the antibody conjugate further comprising a bound diagnostic or therapeutic agent for detecting, imaging or treating the infection. Polyspecific composite conjugates enhance the efficacy of the method, which is especially useful for treating infections that are refractory towards systemic chemotherapy.

CLM What is claimed is:

1. A method of targeting a therapeutic agent to a focus of infection, which comprises parenterally injecting a patient infected with a pathogen with an effective amount of a polyspecific antibody-therapeutic agent conjugate; wherein said conjugate comprises an immunoreactive composite of a plurality of chemically-linked antibodies or antibody fragments which specifically binds to a plurality of accessible epitopes on a single species of pathogen or of an antigen shed by said pathogen or resulting from the fragmentation or destruction of said pathogen and which is accreted at said focus of infection, wherein said polyspecific antibody conjugate further comprises a chemically bound therapeutic agent for treating said infection.

2. The method of claim 1, wherein said agent is a therapeutic radioisotope or boron addend.

3. The method of claim 1, wherein said agent is an anti-pathogenic drug or **cytotoxic** agent.

4. The method of claim 1, wherein said accessible epitopes are not saturated or blocked by the patient's native antibodies.

5. The method of claim 4, wherein said polyspecific antibody conjugate comprises chemically-linked monoclonal antibodies or antigen-binding fragments thereof.

6. The method of claim 1, wherein said polyspecific antibody conjugate is a conjugate of an antiserum or is a conjugate of antibody fragments of an antiserum which specifically bind a plurality of epitopes on a single species of pathogen.

7. The method of claim 6, wherein said antiserum is affinity purified by removal of antibodies which bind to antigens associated with said pathogen circulating at a significant level in the patient's bloodstream.

8. The method of claim 6, wherein said antiserum is affinity purified by contact with bound pathogen or pathogen-associated antigens, and subsequent recovery of antiserum enriched in antibodies that bind to said pathogen or pathogen-associated antigens.

9. The method of claim 1, wherein said pathogen is a protozoan.

10. The method of claim 9, wherein said protozoan is selected from the group consisting of Plasmodium falciparum, Plasmodium vivax, Toxoplasma gondii, Trypanosoma rangeli, Trypanosoma cruzi, Trypanosoma rhodesiensei, Trypanosoma brucei, Schistosoma mansoni, Schistosoma japanicum, Babesia bovis, Elmeria tenella, Onchocerca volvulus, Leishmania tropica, Trichinella spiralis, Onchocerca volvulus, Theileria parva, Taenia hydatigena, Taenia ovis, Taenia saginata, Echinococcus granulosus and Mesocestoides corti.

11. The method of claim 1, which further comprises administering to said patient, at a time after administration of said conjugate sufficient to optimize uptake of said conjugate at the site of said infection, an amount of a second antibody that specifically binds to said conjugate sufficient to reduce the amount of said conjugate in circulation by 10-85% within 2-72 hours.

12. The method of claim 1, wherein said agent is a therapeutic

antibiotic or **cytotoxic** agent that causes hematopoietic toxicity as a side effect of its administration, and wherein said method further comprises administering to said patient, at a ltime prior to, concomitant with or subsequent to administration of said therapeutic conjugate, an amount of a cytokine sufficient to mitigate or **prevent** the hematopoietic toxicity of said agent.

13. The method of claim 1, wherein said pathogen is a microbial pathogen or an invertebrate parasite that expresses a diversity of antigens at various stages of its life cycle, and wherein said imunoreactive composite comprises antibodies or antibody fragments which bind to antigens expressed at different stages of the life cycle of said pathogen or said parasite.

14. The method of claim 13, wherein said th erapeutic agent is sel ected from the group consisting of a therapeutic radioisotope, a boron addend, an anti-pathogenic drug and a **cytotoxic** agent.

15. The method of claim 13, wherein said epitopes are not saturated or blocked by the patient's native antibodies.

16. The method of claim 13, wherein said polyspecific antibody conjugate comprises chemically-linked monoclonal antibodies or antigen-binding fragments thereof.

17. The method of claim 13, wherein said polyspecific antibody conjugate is a conjugate of an antiserum or is a conjugate of antibody fragments of an antiserum which specifically bind a plurality of epitopes on a single species of pathogen.

18. The method of claim 17, wherein said antiserum is affinity purified by the removal of antibodies which bind to antigens associated with said pathogen circulating at a significant level in the patient's bloodstream; and/or by contact with bound pathogen or pathogen-associated antigens, and subsequent recovery of antiserum enriched in antibodies that bind to said pathogen or pathogen-associated antigens.

19. The method of claims 13, wherein said pathogen is a protozoan selected from the group consisting of Plasmodium falciparum, Plasmodium vivax, Toxoplasma gondii, Txypanosoma rangeli, Trypanosoma cruzi, Trypanosoma rhodesiensei, Trypanosoma brucei, Schistosoma mansoni, Schistosoma japanicum, Babesia bovis, Elmeria tenella, Onchocerca volvulus, Leishmania tropica, Trichinella spiralis, Theileria parva, Taenia hydatigena, Taenia ovis, Taenia saginata, Echinococcus granulosus and Mesocestoides corti.

20. The method of claim 13, wherein said pathogen is a helminth or a malarial parasite.

21. The method of claim 13, wherein said therapeutic agent is an antibiotic or **cytotoxic** agent that causes hematopoietic toxicity as a side effect of its administration, and wherein said method further comprises the step of administering to said patient at a time prior to, concomitant with or subsequent to the administration of said therapeutic conjugate, an amount of a cytokine sufficient to mitigate or **prevent** the hematopoietic toxicity of said agent.

22. The method of claim 1, wherein said pathogen is a virus.

23. The method of claim 22, wherein said virus is an RNA virus.

24. The method of claim 22, wherein said virus is a **DNA** virus.

25. The method of claim 22, wherein said virus is selected from the group consisting of the **human immunodeficiency virus** (HIV),

herpes virus, cytomegalovirus, rabies virus, influenza virus, hepatitis B virus, Sendai virus, feline leukemia virus, Reo virus, polio virus, human serum parvo-like virus, simian virus 40, respiratory syncytial virus, mouse mammary tumor virus, Varicella-Zoster virus, Dengue virus, rubella virus, measles virus, adenovirus, human T-cell leukemia viruses, Epstein-Barr virus, murine leukemia virus, mumps virus, vesicular stomatitis virus, Sindbis virus, lymphocytic choriomeningitis virus, wart virus, and blue tongue virus.

26. The method of claim 1, wherein said pathogen is bacterium.

27. The method of claim 26, wherein said bacterium is selected from the group consisting of Streptococcus agalactiae, Legionella pneumophilia, Streptococcus pyogenes, Escherichia coli, Neisseria gonorrhosae, Neisseria meningitidis, Pneumococcus, Hemophilus influenzae B, Treponema pallidum, Lyme disease spirochetes, Pseudomonas aeroginosa, Mycobacterium leprae, Brucella abortus, Mycobacterium tuberculosis, and Tetanus toxin.

28. The method of claim 1, wherein pathogen is a helminth.

29. The method of claim 1, wherein said pathogen is mycoplasma.

30. The method of claim 29, wherein said mycoplasma is selected from the group consisting of Mycoplasma arthritidis, M. hyorhinis, M. orale, M. arginini, Acholeplasma laidlawii, M. salivarum, and M. pneumoniae.

31. The method of claim 1, wherein said pathogen is a fungus.

L27 ANSWER 16 OF 33 USPATFULL on STN
2001:202380 Oligonucleotides which specifically bind retroviral nucleocapsid proteins.
Rein, Alan, Columbia, MD, United States
Casas-Finet, Jose, Gaithersburg, MD, United States
Fisher, Robert, Sharpsburg, MD, United States
Fivash, Matthew, Frederick, MD, United States
Henderson, Louis E., Mount Airy, MD, United States
The United States of America as represented by the Secretary of the Department of Health and Human Services, Washington, DC, United States (U.S. government)
US 6316190 B1 20011113
WO 9744064 19971127
APPLICATION: US 1999-180903 19990712 (9) <--
WO 1997-US8936 19970519 19990712 PCT 371 date 19990712 PCT 102(e) date<--
PRIORITY: US 1996-17128P 19960520 (60)
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention provides oligonucleotides which bind to retroviral nucleocapsid proteins with high affinity, molecular decoys for retroviral nucleocapsid proteins which inhibit viral replication, targeted molecules comprising high affinity oligonucleotides, assays for selecting test compounds, and related kits.

CLM What is claimed is:
1. A targeted molecule comprising an oligonucleotide which binds to a retroviral nucleocapsid protein with high affinity, and a fusion partner, wherein the targeted molecule binds to the retroviral nucleocapsid protein with high affinity.

2. The targeted molecule of claim 1, wherein the fusion partner chemically reacts with the retroviral nucleocapsid protein, thereby reducing the ability of the nucleocapsid protein to package retroviral RNA.

3. The targeted molecule of claim 1, wherein the fusion partner is **cytotoxic**.

4. The targeted molecule of claim 1, wherein the fusion partner is a protein.

5. The targeted molecule of claim 1, wherein the oligonucleotide is a GT rich **DNA** oligonucleotide, or a GU rich RNA oligonuclotide.

6. The targeted molecule of claim 1, wherein the oligonucleotide is selected from the group consisting of a tetranucleotide, a pentanucleotide, a hexanucleotide, a heptanucleotide and an octanucleotide.

7. The targeted molecule of claim 1, wherein the oligonucleotide comprises a sequence selected from the group of sequences consisting of SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, and SEQ ID NO:11.

8. The targeting molecule of claim 1, wherein the targeted molecule binds to **HIV**-1 nucleocapsid (NC) with high affinity.

9. The targeting molecule of claim 1, wherein the fusion partner is a label.

10. The targeting molecule of claim 1, wherein the targeting molecule further comprises a label.

11. The targeted molecule of claim 1, wherein the fusion partner is selected from the group consisting of: disulfides having the formula R--S--S--R; maleimides having the formula ##STR3## α-halogenated ketones having the formula ##STR4## nitric oxide and derivatives containing the NO group; hydrazides having the formula R--NH--NH--R; nitroso compounds having the formula R--NO; cupric ions and complexes containing Cu^{+2} ; ferric ions and complexes containing Fe^{+3} ; and alkylating agents; wherein R can be any atom or molecule, and X is a halogen selected from the group consisting of I, F, Br and Cl.

12. A recombinant **nucleic acid** which encodes an oligonucleotide which binds to a retroviral nucleocapsid protein with high affinity, wherein the **nucleic acid** comprises a promoter which directs expression of the oligonucleotide in a mammalian cell.

13. The **nucleic acid** of claim 12, wherein the **nucleic acid** is packaged in a viral vector.

14. The **nucleic acid** of claim 12, wherein the **nucleic acid** is packaged in a retroviral vector.

15. A cell comprising the **nucleic acid** of claim 12.

16. The cell of claim 15, wherein the cell is a human cell.

17. The cell of claim 15, wherein the cell is a human stem cell.

18. The cell of claim 15, wherein the cell is a human CD4+ cell.

19. A composition comprising a molecular decoy, the molecular decoy comprising an oligonucleotide which binds to a retroviral nucleocapsid protein with high affinity.

20. The composition of claim 19, wherein the molecular decoy is an oligonucleotide with a sequence selected from the group of sequences consisting of SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, and SEQ ID NO:11.

21. The composition of claim 19, further comprising a protein selected from the group consisting of a nucleocapsid protein, and a Gag protein,

wherein the protein is bound to the oligonucleotide.

22. The composition of claim 19, further comprising a pharmaceutical excipient.

23. An assay for detecting target molecules which inhibit binding of an oligonucleotide to a retroviral nucleocapsid protein comprising: providing a retroviral nucleocapsid protein; providing an oligonucleotide which binds to the retroviral nucleocapsid protein with high affinity; providing a target molecule; mixing the retroviral nucleocapsid protein, oligonucleotide and target molecule; and, measuring the inhibitory effect of the target molecule on oligonucleotide binding to the retroviral nucleocapsid protein.

24. The assay of claim 23, wherein the oligonuclcotide is labeled.

25. The assay of claim 23, wherein the target molecule is selected from the group consisting of oligonucleotides and peptides.

26. The assay of claim 23, wherein the oligonucleotide, target molecule and retroviral protein are mixed in an aqueous solution.

27. The assay of claim 23, wherein the inhibitory effect of the target molecule is measured by plasmon resonance.

28. The assay of claim 23, wherein the assay further comprises parallel analysis of a second target molecule by performing the steps of providing a retroviral nucleocapsid protein; providing an oligonucleotide which binds to the retroviral nucleocapsid protein with high affinity; providing a second target molecule; independently mixing the second target molecule with the retroviral nucleocapsid protein and oligonucleotide; and, measuring the inhibitory effect of the target molecule on oligonucleotide binding to the retroviral nucleocapsid protein.

29. The assay of claim 28, wherein the second target molecule, retroviral nucleocapsid protein and oligonucleotide are mixed in a well on a microtiter tray.

30. A method of detecting a nucleocapsid (NC) protein comprising binding an NC-specific oligonucleotide to the NC protein, thereby forming an NC-oligonuclcotide complex, and detecting the complex, thereby detecting the NC protein.

31. The method of claim 30, wherein the oligonucleotide comprises a detectable label and detection of the NC-oligonucleotide complex is performed by detecting the detectable label.

32. The method of claim 30, wherein the NC protein is a component of an intact retrovirus.

33. The method of claim 30, wherein the NC protein is a Gag precursor protein.

34. The method of claim 30, wherein the NC protein is derived from **HIV**-1.

35. A method of purifying an NC protein comprising binding an NC-specific oligonucleotide to the NC protein, thereby forming an NC-oligonucleotide complex, and purifying the complex, thereby purifying the NC protein.

36. The method of claim 35, wherein the NC protein is a component of an intact retrovirus.

37. The method of claim 35, wherein the oligonucleotide is linked to a

magnetic bead.

L27 ANSWER 17 OF 33 USPATFULL on STN
2001:158482 Method of eliminating inhibitory/instability regions of mRNA.
Pavlakis, George N., Rockville, MD, United States
Felber, Barbara K., Rockville, MD, United States
The United States of America as represented by the Department of Health and Human Services, Washington, DC, United States (U.S. corporation)
US 6291664 B1 20010918
APPLICATION: US 1999-414117 19991008 (9) <--
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method of locating an inhibitory/instability sequence or sequences within the coding region of an mRNA and modifying the gene encoding that mRNA to remove these inhibitory/instability sequences by making clustered nucleotide substitutions without altering the coding capacity of the gene is disclosed. Constructs containing these mutated genes and host cells containing these constructs are also disclosed. The method and constructs are exemplified by the mutation of a **Human Immunodeficiency Virus**-1 Rev-dependent gag gene to a Rev independent gag gene. Constructs useful in locating inhibitory/instability sequences within either the coding region or the 3' untranslated region of an mRNA are also disclosed. The exemplified constructs of the invention may also be useful in **HIV**-1 immunotherapy and immunoprophylaxis.

CLM What is claimed is:
1. A **nucleic acid** construct, wherein said **nucleic acid** construct comprises a **nucleic acid** sequence capable of producing **HIV** Env protein in the absence of **HIV** Rev protein, and wherein said **nucleic acid** sequence comprises multiple point mutations which decrease the effect of an inhibitory/instability sequence which is present in the corresponding **nucleic acid** sequence of the native IRV env gene between nucleotides selected from the group consisting of 5606 and 6014; 6004 and 6435; 6435 and 6878; 6879 and 7266; 7266 and 7924; 8021 and 8561; 5606 and 6435; 5606 and 6878; and 6879 and 7924; using the using the numbering of the nucleotide sequence of the **HIV**-1 molecular clone pHXB2.

2. A **nucleic acid** construct of claim 1 wherein said **nucleic acid** construct comprises multiple point mutations between nucleotides selected from the group consisting of 7266 and 7924; 5606 and 6878; and 6879 and 7924; using the numbering of the nucleotide sequence of the **HIV**- 1 molecular clone pHXB2.

3. A **nucleic acid** construct of claim 1 wherein said **nucleic acid** construct comprises one or more sequences selected from the group consisting of CTTGGGATGcTGATGATcTGcAGcGcCAcCGAgAAgcTGTGGGTC (SEQ ID NO: 76) at positions 5834-5878; ATTATGGcGTgCCcGTGTGGAAG (SEQ ID NO: 78) at positions 5886-5908; CACTCTATTcTGcGCcTCcGAcGCcAAgGCATATGAT (SEQ ID NO: 80) at positions 5920-5956; ACAGAGGTgCAcAAcGTcTGGGCCAC (SEQ ID NO: 82) at positions 5957-5982; CCAACCCcCAgGAgGTgGTgcTGGTgAAcGTGACcGAgAAcTTcAACA TGTG (SEQ ID NO: 84) at positions 6006-6057; TAACCCCcCTCTGcGTgAGccTgAAGTGCACcGAccTGAAGAATG (SEQ ID NO: 86) at positions 6135-6179; ATCAGCACcAGCATccGcGGcAAGGTGCAG (SEQ ID NO: 88) at positions 6251-6280; GAATATGCcTTcTTcTAcAAgCTgGATATAATA (SEQ ID NO: 90) at positions 6284-6316; CCAATAGcTAAgGAcACcACCAGCTAT (SEQ ID NO: 92) at positions 6317-6343; GCCCCGGCcGGcTTcGCGATcCTgAAgTGcAAcAAcAAGACGTTC (SEQ ID NO: 94) at positions 6425-6469; CAACTGCTGcTgAAcGGCAGcCTgGCcGAgGAgGAGG TAGTA (SEQ ID NO: at positions 6542-6583; TCTGCCAAcTTCACcGACAAcGCcAAgACC ATAAT (SEQ ID NO: 98) at positions 6590-6624; CTGAACCAgTCcGTgGAgATcAAcTGTACAAG (SEQ ID NO: 100) at positions 6632-6663; CAACAACAAcACcGGcAAgcGcATCCGTATC (SEQ ID NO: 102) at positions 6667-6697; GCTAGCAAgcTgcGcGAgCAgTAcGGgAAcAAcAAgACcATAATCTT (SEQ ID NO: 104) at positions 6806-6852; TTCTACTGgAAcTCcACcCAgCTGTTcAAcAGcACcTGGTTTA AT (SEQ ID NO: 106) at positions 6917-6961; CACAATCACcCTgCCcTGCcGcATcAAgCAgATcATAAACATG (SEQ ID NO: 108) at

positions 7000-7040; CATCAGCGGCCAgATCCGCTGCTCCTCCAACATCACCGGGCTGCTA (SEQ ID NO: 110) at positions 7084-7129; GAGGGACAAcTGGAGgAGcGAgcTgTAcAAgTAcAA gGTgGTgAAgATcGAA CCATTA (SEQ ID NO: 112) at positions 7195-7252; GCCTTGGAAcGCcAGcTGGAGcAAcAAgTCcCTGGAACAG (SEQ ID NO: 114) at positions 7594-7633; GAGTGGGACcGcGAgATcAACAAcTACACAAG (SEQ ID NO: 116) at positions 7658-7689; ATACACTCCcTgATcGAgGAgTCcCAgAACCAgCAgGAgAAGAATGAA (SEQ ID NO: 118) at positions 7694-7741; CAGGCCCGAgGGcATcGAgGAgGAgGGcGGc GAGAGAGAC (SEQ ID NO: 120) at positions 7954-7993; TACCACCGCcTGcGcGACcTgCTCcTGATcGTgACGAGGATcGTGGAACT (SEQ ID NO: 122) at positions 8072-8121; GGTGGGAgGCCCTCAAgTAcTGGTGGAAeCTCCTcCAGTATTGG (SEQ ID NO: 124) at positions 8136-8179; and AGTCAGGAgCTgAAGAAcAGcGCcGTgAaCcT GCTCAATG (SEQ ID NO: 126) at positions 8180-8219; using the numbering of the nucleotide sequence of the **HIV**-1 molecular clone pHXB2.

4. A **nucleic acid** construct of claim 1 wherein said **nucleic acid** construct comprises one or more sequences selected from the group consisting of GAATAGTGCTGTTAACCTCCTGAACGCTACCGCTATCGCCGTGGCGGA AGGAACCGACAGGGTTATAG (SEQ ID NO: 10) at nucleotides 8194-8261; AAGTATTACAAGCCGCCTACCGCGCCATCAGACATATCCCCCGCCGCA TCCGCCAGGGCTTG (SEQ ID NO: 11) at nucleotides 8262-8323; GCTATAAGATGGGCGGTAAATGGAGCAAGTCCTCCGTC ATCGGCTGGC CTGCTGTAAG (SEQ ID NO: 12) at nucleotides 8335-8392; GGAAAGAATGCGCAGGGCCGAACCCGCCGCCGACGGAGTTGGCGCCG TATCTCGAGAC (SEQ ID NO: 13) at nucleotides 8393-8450; CTAGAAAAACACGGCGCCATTACCTCCTCTAACACCGCCGCC AATAAC GCCGCTTGTGCCTG (SEQ ID NO: 14) at nucleotides 8451-8512; and GCTAGAAGCACAGGAAGAAGAGGAAGTCGGCTTCCCCGTTACCCCTCA GGTACCTTTAAG (SEQ ID NO: 15) at nucleotides 8513-8572; using the numbering of the nucleotide sequence of the **HIV**-1 molecular clone pHB2.

5. A vector comprising a **nucleic acid** construct of claim 1.

6. A vector comprising a **nucleic acid** construct of claim 2.

7. A vector comprising a **nucleic acid** construct of claim 3.

8. A vector comprising a **nucleic acid** construct of claim 4.

9. A host cell comprising a **nucleic acid** construct of claim 1.

10. A host cell comprising a **nucleic acid** construct of claim 2.

11. A host cell comprising a **nucleic acid** construct of claim 3.

12. A host cell comprising a **nucleic acid** construct of claim 4.

13. A composition comprising a **nucleic acid** construct of claim 1 and a carrier.

14. A composition comprising a **nucleic acid** construct of claim 2 and a carrier.

15. A composition comprising a **nucleic acid** construct of claim 3 and a carrier.

16. A composition comprising a **nucleic acid** construct of claim 4 and a carrier.

17. A **nucleic acid** construct, wherein said **nucleic acid** construct comprises a **nucleic acid** sequence capable of producing **HIV** Pol protein in the absence of **HIV** Rev protein, and wherein said **nucleic acid** sequence comprises multiple point mutations which decrease the effect of an inhibitory/instability sequence which is present in the corresponding **nucleic acid** sequence of the native **HIV** pol gene which is present between nucleotides 3700-4194 using the numbering system of pHXB2.

18. A **nucleic acid** construct of claim 17 wherein said **nucleic**

acid construct comprises the sequences GGAATATGGCAgCTgGACTGCACgCACCTgG AgGGgAAgGTgATCCTGGTA G (SEQ ID NO: 67) at nucleotides 39504001 and TGGCCAGTAAAAACAATACAcACgGACAAcGGaAGCAAcTTCACtGGTGC TACGG (SEQ ID NO: 74) at nucleotides 4097-4151; using the numbering of the nucleotide sequence of the **HIV**-1 molecular clone pHXB2.

19. A **nucleic acid** construct, wherein said **nucleic acid** construct comprises a **nucleic acid** sequence capable of producing **HIV** Pol protein in the absence of **HIV** Rev protein, and wherein said **nucleic acid** sequence comprises the sequence CCCCTCGTCACAgTAAgGATcGGGGGCAACTcAAGGAAGCgCTgcTcGATACAGGAG (SEQ ID NO: 43) at nucleotides 1823-1879, using the numbering of the nucleotide sequence of the **HIV**-1 molecular clone pHXB2.

20. A vector comprising a **nucleic acid** construct of claim 17.

21. A vector comprising a **nucleic acid** construct of claim 18.

22. A vector comprising a **nucleic acid** construct of claim 19.

23. A host cell comprising a **nucleic acid** construct of claim 17.

24. A host cell comprising a **nucleic acid** construct of claim 18.

25. A host cell comprising a **nucleic acid** construct of claim 19.

26. A composition comprising a **nucleic acid** construct of claim 17 and a carrier.

27. A composition comprising a **nucleic acid** construct of claim 18 and a carrier.

28. A composition comprising a **nucleic acid** construct of claim 19 and a carrier.

29. A composition according to any one of claims 13 to 16, wherein said composition is useful for inducing antibodies which react with **HIV** Env protein in a mammal; said carrier is a pharmaceutically acceptable carrier for administering to a mammal; and said **nucleic acid** construct is present in an amount which is capable of expressing **HIV** Env protein in an amount which is effective to induce said antibodies in said mammal.

30. A composition according to any one of claims 13 to 16, wherein said composition is useful for inducing **cytotoxic** T lymphocytes in a mammal; said carrier is a pharmaceutically acceptable carrier; and said **nucleic acid** construct is present in an amount which is capable of expressing **HIV** Env protein in an amount which is effective to induce said **cytotoxic** T lymphocytes in said mammal.

31. A composition according to any one of claims 26 to 28, wherein said composition is useful for inducing antibodies which react with **HIV** Pol protein in a mammal; said carrier is a pharmaceutically acceptable carrier; and said **nucleic acid** construct is present in an amount which is capable of expressing **HIV** Pol protein in an amount which is effective to induce said antibodies in said mammal.

32. A composition according to any one of claims 26 to 28, wherein said composition is useful for inducing **cytotoxic** T lymphocytes in a mammal, said carrier is a pharmaceutically acceptable carrier; and said **nucleic acid** construct is present in an amount which is capable of expressing **HIV** Pol protein in an amount which is effective to induce said **cytotoxic** T lymphocytes in said mammal.

33. A method for inducing antibodies in a mammal comprising administering to a mammal a composition of claim 29.

34. A method for inducing **cytotoxic** T lymphocytes in a mammal comprising administering to a mammal a composition of claim 30.

35. A method for inducing antibodies in a mammal comprising administering to a mammal a composition of claim 31.

36. A method for inducing **cytotoxic** T lymphocytes in a mammal comprising administering to a mammal a composition of claim 32.

37. A **nucleic acid** construct comprising a **nucleic acid** sequence capable of producing SIV Gag protein in the absence of Rev protein, wherein said **nucleic acid** sequence comprises multiple point mutations which decrease the effect of an inhibitory/instability sequence which is present in the corresponding **nucleic acid** sequence of the native SIV gag gene.

38. A vector comprising a **nucleic acid** construct of claim 37.

39. A host cell comprising a **nucleic acid** construct of claim 37.

40. A composition comprising a **nucleic acid** construct of claim 37.

41. A **nucleic acid** construct comprising a **nucleic acid** sequence capable of producing SIV Env protein in the absence of Rev protein, wherein said **nucleic acid** sequence comprises multiple point mutations which decrease the effect of an inhibitory/instability sequence which is present in the corresponding **nucleic acid** sequence of the native SIV env gene.

42. A vector comprising a **nucleic acid** construct of claim 41.

43. A host cell comprising a **nucleic acid** construct of claim 41.

44. A composition comprising a **nucleic acid** construct of claim 41.

45. A **nucleic acid** construct comprising a **nucleic acid** sequence capable of producing SIV Pol protein in the absence of Rev protein, wherein said **nucleic acid** sequence comprises multiple point mutations which decrease the effect of an inhibitory/instability sequence which is present in the corresponding **nucleic acid** sequence of the native SIV pol gene.

46. A vector comprising a **nucleic acid** construct of claim 45.

47. A host cell comprising a **nucleic acid** construct of claim 45.

48. A composition comprising a **nucleic acid** construct of claim 45.

L27 ANSWER 18 OF 33 USPATFULL on STN
2001:75179 Nucleic acid constructs containing genes encoding transport signals.
Sedlacek, Hans-Harald, Marburg, Germany, Federal Republic of
Mueller, Rolf, Marburg, Germany, Federal Republic of
Luehrmann, Reinhard, Marburg, Germany, Federal Republic of
Aventis Pharma Deutschland GmbH, Frankfurt am Main, Germany, Federal Republic of (non-U.S. corporation)
US 6235526 B1 20010522
APPLICATION: US 1997-850744 19970502 (8) <--
PRIORITY: DE 1996-19617851 19960503
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Nucleic acid constructs are disclosed which possess a nuclear retention signal which is linked, downstream in the reading direction, to a transgene. The nuclear retention signal can regulate the presence of the transcription product in the cell nucleus or else the intracellular

transport of the transcription product.

CLM What is claimed is:

1. A **nucleic acid** construct comprising: (i) a nuclear retention signal selected from the group consisting of a rev-responsive element (RRE) of Human Immune Deficiency Virus-1 (**HIV**-1), an RRE of Human Immune Deficiency Virus-2 (**HIV**-2), an RRE-equivalent retention signal of a retrovirus and an RRE-equivalent retention signal of Hepatitis B virus (HBV), wherein said nuclear retention signal is operably linked to a transgene; (ii) a first promoter sequence or enhancer sequence which activates basal transcription of the transgene; (iii) a second promoter or enhancer sequence which activates basal transcription of a nuclear export factor, wherein at least one of said first or second promoter sequences or enhancer sequences is a chimeric promoter which interacts with an adjacent, upstream, cell-specifically, virus-specifically or metabolically activatable activator sequence which influences the expression of said transgene; and (iv) a **nucleic acid** which encodes a nuclear export factor selected from the group consisting of a rev gene of **HIV**-1, a rev gene of **HIV**-2, a rev gene of maedi-visna virus, a rev gene of caprine arthritis encephalitis virus, a rev gene of equine infectious anemia virus, a rev gene of feline immunodeficiency virus, a rev gene of retroviruses and a rev gene of HTLV, wherein said nuclear export factor binds to a transcription product of the nuclear retention signal and thereby mediates transport of said transcription product of the transgene out of a cell's nucleus and into the cell's cytoplasm.

2. A **nucleic acid** construct as claimed in claim 1 wherein a 5' end of the nuclear retention signal is linked directly or indirectly to a 3' end of the transgene.

3. A **nucleic acid** construct as claimed in claim 1 wherein a transcription product of the nuclear retention signal possesses a structure for binding to a nuclear export factor selected from the group consisting of a rev-gene of the viruses **HIV**-1, **HIV**-2, maedi-visna virus, caprine arthritis encephalitis virus, equine infectious anemia virus, feline immunodeficiency virus, and HTLV.

4. A **nucleic acid** construct as claimed in claim 1 wherein the first promoter sequence or enhancer sequence and the second promoter sequence or enhancer sequence are the same or different, but at least one is nonspecifically, cell-specifically, virus-specifically, metabolically, or cell-cycle-specifically activatable.

5. A **nucleic acid** construct as claimed in claim 1, wherein the chimeric promoter inhibits the expression of said transgene.

6. A **nucleic acid** construct as claimed in claim 1, wherein the **nucleic acid** is **DNA**.

7. A **nucleic acid** construct as claimed in claim 1, wherein the **nucleic acid** construct is a vector.

8. A **nucleic acid** construct as claimed in claim 1, wherein the transgene is a structural gene which encodes a therapeutically active compound selected from the group consisting of cytokines; growth factors; antibodies; antibody fragments; fusion proteins composed of a ligand and an enzyme; fusion proteins composed of a ligand and a cytokine; fusion proteins composed of a ligand and a growth factor; receptors for cytokines; receptors for growth factors; proteins having an antiproliferative effect; proteins having an apoptotic effect; proteins having a **cytotoxic** effect; angiogenesis inhibitors; thrombosis-inducing proteins; blood coagulation factor; coagulation inhibitors; fibrinolysis-inducing protein; complement-activating proteins; human C3b; modified C3b; bacterial proteins; virus coat proteins; parasitic antigens; peptides having an effect on the blood circulation; proteins having an effect on the blood circulation; and ribozymes.

9. A **nucleic acid** construct as claimed in claim 1 wherein the transgene is a structural gene which encodes a ribozyme which inactivates mRNA encoding a protein selected from the group consisting of cell-cycle control proteins, virus proteins, cytokines, growth factors, cytokine receptors and growth factor receptors.

10. A **nucleic acid** construct as claimed in claim 1 wherein the transgene is a structural gene which encodes an enzyme which cleaves a precursor of a drug, thereby forming the drug.

11. A **nucleic acid** construct as claimed in claim 1 wherein the transgene is a structural gene which encodes a ligand-enzyme fusion protein.

12. An isolated cell containing a **nucleic acid** construct as claimed in claim 1.

13. A cell transformed with a **nucleic acid** construct as claimed in claim 1.

14. A **nucleic acid** construct as claimed in claim 1, wherein the chimeric promoter is a promoter module selected from the group consisting of CDE-CHR and E2FBS-CHR.

15. A **nucleic acid** construct as claimed in claim 1, wherein the promoter sequence, enhancer sequence or activator sequence is selected from the group consisting of gene-regulatory nucleotide sequences which are activated in endothelial cells, smooth muscle cells, striated muscle cells, macrophages, lymphocytes, tumor cells, liver cells, leukemia cells and glia cells, or is selected from the group consisting of promoter sequences of HBV, HCV, HSV, HPV, EBV, HTLV, and **HIV** viruses.

16. A **nucleic acid** construct as claimed in claim 1, wherein the nuclear retention signal is an RRE sequence and the nuclear export factor is a rev protein.

17. A **nucleic acid** construct as claimed in claim 4 wherein said at least one promoter sequence or enhancer sequence is metabolically activatable by hypoxia.

18. A **nucleic acid** construct as claimed in claim 7, which is a plasmid vector.

19. A **nucleic acid** construct as claimed in claim 7, which is a viral vector.

20. A **nucleic acid** construct as claimed in claim 9, wherein the cell-cycle control protein is selected from the group consisting of cyclin A, cyclin B, cyclin D1, cyclin E, E2F1-5, cdc2, cdc25C, and DP1.

21. A **nucleic acid** construct as claimed in claim 11, wherein the ligand binds to proliferating endothelial cells and is selected from the group consisting of antibodies, antibody fragments, terminal mannose-containing proteins, cytokines, growth factors, and adhesion molecules.

22. A **nucleic acid** construct as claimed in claim 11, wherein the ligand binds to tumor cells.

23. A **nucleic acid** construct comprising: (i) a nuclear retention signal selected from the group consisting of a rev-responsive element (RRE) of Human Immune Deficiency Virus-1 (**HIV**-1), an RRE of Human Immune Deficiency Virus-2 (**HIV**-2), an RRE-equivalent retention signal of a retrovirus and an RRE-equivalent retention signal of Hepatitis B virus (HBV), wherein said nuclear retention signal is operably linked to

a transgene; (ii) a first promoter sequence or enhancer sequence which activates basal transcription of the transgene; (iii) a second promoter sequence or enhancer sequence which activates transcription of a nuclear export factor, wherein at least one of said first or second promoter sequences or enhancer sequences comprises an activator-responsive promoter unit having the following components: a) at least a third promoter sequence or enhancer sequence which is non-specifically, virus-specifically, metabolically, cell-specifically and/or cell-cycle-specifically activatable, b) at least one activator sequence which is located downstream of the third promoter sequence or enhancer sequence and is activated by the third promoter sequence or enhancer sequence, and c) an activator-responsive promoter which is activated by the expression products of said at least one activator sequence; and iv) a **nucleic acid** which encodes a nuclear export factor selected from the group consisting of a rev gene of **HIV**-1, a rev gene of **HIV**-2, a rev gene of maedi-visna virus, a rev gene of caprine arthritis encephalitis virus, a rev gene of equine infectious anemia virus, a rev gene of feline immunodeficiency virus, a rev gene of retroviruses and a rev gene of HTLV, wherein said nuclear export factor binds to a transcription product of the nuclear retention signal and thereby mediates transport of said transcription product of the transgene out of a cell's nucleus and into the cell's cytoplasm.

24. A **nucleic acid** construct as claimed in claim 23, wherein the first and/or second promoter sequence or enhancer sequence and/or the activator-responsive promoter is a chimeric promoter and said at least one activator sequence is a gene encoding at least one transcription factor which activates the chimeric promoter.

25. A **nucleic acid** construct as claimed in claim 23, wherein the activator-responsive promoter is a LexA operator in combination with a SV40 promoter, and said at least one activator sequence comprises a cDNA encoding LexA **DNA**-binding protein, whose 3' end is linked to a 5' end of a cDNA encoding Gal80 protein, said construct further comprising a second activator sequence comprising a cDNA encoding a Gal80-binding domain of Gal4 protein, whose 3' end is linked to a 5' end of a cDNA of SV40 large T antigen nuclear localization signal, whose 3' end is linked to a 5' end of a cDNA encoding a HSV-1 VP16 transactivating domain.

26. A **nucleic acid** construct as claimed in claim 23 wherein the activator-responsive promoter has one or more sequences for binding to a Gal4 protein in combination with at least one SV40 promoter and said at least one activator sequence has a cDNA encoding a **DNA**-binding domain of the Gal4 protein and a cDNA encoding Gal80, said construct further comprising a second activator sequence having a cDNA encoding a Gal80-binding domain of Gal4, a cDNA encoding SV40 nuclear localization signal and a cDNA encoding an HSV-1 VP16 acid transactivating domain.

27. A **nucleic acid** construct as claimed in claim 23 wherein said at least one activating sequence has a cDNA encoding SV40 nuclear localization signal; a cDNA encoding an HSV-1 VP16 acid transactivating domain; and a cDNA encoding a cytoplasmic moiety of a CD4 glycoprotein, said construct further comprising a second activating sequence having a cDNA encoding SV40 nuclear localization signal, a cDNA encoding a **DNA**-binding domain of a Gal4 protein and a cDNA encoding a CD4-binding sequence of p56 lck protein.

28. A **nucleic acid** construct as claimed in claim 23 wherein the promoter sequence, enhancer sequence or activator sequence is selected from the group consisting of gene-regulatory nucleotide sequences which are activated in endothelial cells, smooth muscle cells, striated muscle cells, macrophages, lymphocytes, tumor cells, liver cells, leukemia cells and glia cells, or is selected from the group consisting of promoter sequences of HBV, HCV (Hepatitis C virus), HSV (Herpes simplex virus), HPV (Human papilloma virus), EBV (Epstein-Barr virus), HTLV or **HIV** viruses.

29. A **nucleic acid** construct as claimed in claim 23, wherein a 5' end of the nuclear retention signal is linked directly or indirectly to a 3' end of the transgene.

30. A **nucleic acid** construct as claimed in claim 23, wherein a transcription product of the nuclear retention signal possesses a structure for binding to a nuclear factor selected from the group consisting of a rev-gene of the viruses **HIV**-1, **HIV**-2, maedi-visna virus, caprine arthritis encephalitis virus, equine infectious anemia virus, feline immunodeficiency virus, and HTLV.

31. A **nucleic acid** construct as claimed in claim 23, wherein the first promoter sequence or enhancer sequence and the second promoter sequence or enhancer sequence are the same or different, but at least one is nonspecifically, cell-specifically, virus-specifically, metabolically, or cell-cycle-specifically activatable.

32. A **nucleic acid** construct as claimed in claim 23, wherein at least one of said first or second promoter sequences or enhancer sequences is a chimeric promoter which interacts with an adjacent, upstream, cell-specifically, virus-specifically or metabolically activatable activator sequence which influences the expression of said transgene.

33. A **nucleic acid** construct as claimed in claim 23, wherein the **nucleic acid** is **DNA**.

34. A **nucleic acid** construct as claimed in claim 23, wherein the **nucleic acid** construct is a vector.

35. A **nucleic acid** construct as claimed in claim 23, wherein the transgene is a structural gene which encodes a therapeutically active compound selected from the group consisting of cytokines; growth factors; antibodies, antibody fragments; fusion proteins composed of a ligand and an enzyme; fusion proteins composed of a ligand and a cytokine; fusion proteins composed of a ligand and a growth factor; receptors for cytokines; receptors for growth factors; proteins having an antiproliferative effect; proteins having an apoptotic effect; proteins having a **cytotoxic** effect; angiogenesis inhibitors; thrombosis-inducing proteins; blood coagulation factor; coagulation inhibitors; fibrinolysis-inducing protein; complement-activating proteins; human C3b; modified C3b; bacterial proteins; virus coat proteins; parasitic antigens; peptides having an effect on the blood circulation; proteins having an effect on the blood circulation; and ribozymes.

36. A **nucleic acid** construct as claimed in claim 23, wherein the transgene is a structural gene which encodes a ribozyme which inactivates mRNA encoding a protein selected from the group consisting of cell-cycle control proteins, virus proteins, cytokines, growth factors, cytokine receptors and growth factor receptors.

37. A **nucleic acid** construct as claimed in claim 23, wherein the transgene is a structural gene which encodes an enzyme which cleaves a precursor of a drug, thereby forming the drug.

38. A **nucleic acid** construct as claimed in claim 23, wherein the transgene is a structural gene which encodes a ligand-enzyme fusion protein.

39. An isolated cell containing a **nucleic acid** construct as claimed in claim 23.

40. A cell transformed with a **nucleic acid** construct as claimed in claim 23.

41. A **nucleic acid** construct as claimed in claim 23, wherein the nuclear retention signal is an RRE sequence and the nuclear export factor is a rev protein.

42. A **nucleic acid** construct as claimed in claim 31, wherein said at least one promoter sequence or enhancer sequence is metabolically activatable by hypoxia.

43. A **nucleic acid** construct as claimed in claim 32, wherein the chimeric promoter inhibits the expression of said transgene.

44. A **nucleic acid** construct as claimed in claim 32, wherein the chimeric promoter is a promoter module selected from the group consisting of CDE-CHR and E2FBS-CHR.

45. A **nucleic acid** construct as claimed in claim 34, which is a plasmid vector.

46. A **nucleic acid** construct as claimed in claim 34, which is a viral vector.

47. A **nucleic acid** construct as claimed in claim 36, wherein the cell-cycle control protein is selected from the group consisting of cyclin A, cyclin B, cyclin D1, cyclin E, E2F1-5, cdc2, cdc25C, and DP1.

48. A **nucleic acid** construct as claimed in claim 38, wherein the ligand binds to proliferating endothelial cells and is selected from the group consisting of antibodies, antibody fragments, terminal mannose-containing proteins, cytokines, growth factors, and adhesion molecules.

49. A **nucleic acid** construct as claimed in claim 38, wherein the ligand binds to tumor cells.

L27 ANSWER 19 OF 33 USPATFULL on STN
2000:101881 **Immunogenic** compositions comprising DAL/DAT double-mutant, auxotrophic, attenuated strains of Listeria and their methods of use.
Frankel, Fred R., Philadelphia, PA, United States
Portnoy, Daniel A., Albany, CA, United States
The Trustees of the University of Pennsylvania, Philadelphia, PA, United States (U.S. corporation)
US 6099848 20000808
APPLICATION: US 1997-972902 19971118 (8) <--
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Listeria monocytogenes is an intracellular bacterial pathogen that elicits a strong cellular immune response following infection and therefore has potential use as a **vaccine** vector. However, while infections by L. monocytogenes are fairly rare and can readily be controlled by a number of antibiotics, the organism can nevertheless cause meningitis and death, particularly in immunocompromised or pregnant patients. We therefore have endeavored to isolate a highly attenuated strain of this organism for use as a **vaccine** vector. D-Alanine is required for the synthesis of the mucopeptide component of the cell walls of virtually all bacteria and is found almost exclusively in the microbial world. We have found in L. monocytogenes two genes that control the synthesis of this compound, an alanine racemase gene (dal) and a D-amino acid aminotransferase gene (dat). By inactivating both genes, we produced an organism that could be grown in the laboratory when supplemented with D-alanine but was unable to grow outside the laboratory, particularly in the cytoplasm of eukaryotic host cells, the natural habitat of this organism during infection. In mice, the double-mutant strain was completely attenuated. Nevertheless, it showed the ability, particularly under conditions of transient suppression of

the mutant phenotype, to induce **cytotoxic** T lymphocyte responses and to generate **protective** immunity against lethal challenge by wild-type L. monocytogenes equivalent to that induced by the wild-type organism.

CLM What is claimed is:

1. A method of eliciting a T cell immune response to an antigen in a mammal comprising administering to said mammal an auxotrophic attenuated strain of Listeria which expresses said antigen, wherein said auxotrophic attenuated strain comprises a mutation in both the dal and dat genes in the genome of said Listeria.

2. The method of claim 1, wherein said Listeria is L. monocytogenes.

3. The method of claim 1, wherein said auxotrophic attenuated strain further comprises **DNA** encoding a heterologous antigen.

4. The method of claim 1, wherein said auxotrophic attenuated strain further comprises a vector comprising a **DNA** encoding a heterologous antigen.

5. The method of claim 3, wherein said heterologous antigen is an **HIV**-1 antigen.

6. The method of claim 4, wherein said heterologous antigen is an **HIV**-1 antigen.

7. An **immunogenic** composition that is capable of inducing a strong **CTL** response comprising an auxotrophic attenuated strain of Listeria which expresses an antigen, wherein said auxotrophic attenuated strain comprises a mutation in both the dal and dat genes in the genome of said Listeria.

8. The composition of claim 7, wherein said Listeria is L. monocytogenes.

9. The composition of claim 7, wherein said auxotrophic attenuated strain further comprises **DNA** encoding a heterologous antigen.

10. The composition of claim 7, wherein said auxotrophic attenuated strain further comprises a vector comprising a **DNA** encoding a heterologous antigen.

11. The composition of claim 9, wherein said heterologous antigen is an **HIV**-1 antigen.

12. The composition of claim 10, wherein said heterologous antigen is an **HIV**-1 antigen.

13. An isolated strain of Listeria comprising a mutation in a dal gene and a mutation in a dat gene which render said strain auxotrophic for D-alanine.

14. The isolated strain of Listeria of claim 13, further comprising a heterologous antigen.

L27 ANSWER 20 OF 33 USPATFULL on STN
2000:101880 Chimeric Gag pseudovirions.
Tobin, Gregory J., Frederick, MD, United States
Gonda, Matthew A., Newtown Square, PA, United States
The United States of America as represented by the Department of Health and Human Services, Washington, DC, United States (U.S. government)
US 6099847 20000808
APPLICATION: US 1997-857385 19970515 (8) <--
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention provides, inter alia, recombinant chimeric nucleic

acids encoding a Gag-fs-fusion partner fusion protein; a pseudovirion comprising a retroviral Gag protein and a fusion partner, wherein the fusion partner is present in a Gag-fs-fusion partner fusion protein; an **immunogenic** composition comprising a pseudovirion; a Gag-fs-fusion partner fusion protein; and a method of making the pseudovirions of the present invention.

CLM What is claimed is:

1. A recombinant chimeric **nucleic acid**, comprising: a retroviral gag sequence; a target **nucleic acid** sequence derived from a **nucleic acid** encoding a fusion partner selected from the group consisting of Env, an interleukin, TNF, GM/CSF, a nonretroviral viral antigen and a cancer antigen; wherein the gag and target sequences are transcribed from a single start site of transcription, and wherein the gag and target sequences are in different reading frames; and, a frame-shift site.

2. The recombinant chimeric **nucleic acid** of claim 1, wherein the target **nucleic acid** sequence is derived from a **nucleic acid** encoding a fusion partner selected from the group consisting of IL-1, IL-2, IL-4, IL-6, MART-1, gp 100, tyrosinase, bcl-1, bcl-2, c-myc, int-2, hst-1, ras, p53, prostate-specific membrane antigen, papilloma virus protein L1, protein kinase C., and G proteins.

3. The recombinant chimeric **nucleic acid** of claim 1, wherein the frame shift site is derived from a site selected from the group consisting of a retroviral frame shift site, a retrotransposon frame shift site, a human astrovirus frame shift site, a mouse intracisternal particle frame shift site, an HERV frame shift site, a Ty element frame shift site, and an optimized synthetic frameshift site.

4. A recombinant chimeric gag-env **nucleic acid**, comprising: a retroviral gag sequence; a retroviral env sequence; wherein the gag and env sequences are transcribed from a single start site of transcription, and wherein the gag and env sequences are in different reading frames; and, a retroviral frame-shift site derived from a retroviral gag-pol frame shift site.

5. The recombinant **nucleic acid** of claim 4, wherein the env sequence encodes approximately the carboxyl 65% of Env protein.

6. The recombinant **nucleic acid** of claim 4, wherein the **nucleic acid** further comprises a pol sequence.

7. The recombinant **nucleic acid** of claim 4, wherein the **nucleic acid** is a subsequence in a baculoviral vector.

8. The recombinant **nucleic acid** of claim 4, wherein the **nucleic acid** is competent to produce pseudovirions in an insect cell.

9. The recombinant **nucleic acid** of claim 4, wherein the **nucleic acid** is competent to produce pseudovirions in an insect cell, and wherein the **nucleic acid** hybridizes under stringent conditions to **HIV** Gag-fs-SU.

10. The recombinant **nucleic acid** of claim 4, wherein the **nucleic acid** is **HIV** Gag-fs-SU or a conservative variation thereof.

11. The recombinant **nucleic acid** of claim 4, wherein the **nucleic acid** is **HIV** Gag-fs-SU.

12. The recombinant **nucleic acid** of claim 4, wherein the **nucleic acid** is a subsequence in a baculoviral vector, wherein the vector is competent to transduce an insect cell.

13. The recombinant **nucleic acid** of claim 4, wherein the gag and env sequences are derived from **HIV**.

14. The recombinant **nucleic acid** of claim 4, wherein the **nucleic acid** further comprises a polyhedrin promoter.

15. The recombinant **nucleic acid** of claim 4, wherein the **nucleic acid** further comprises an SV 40 polyadenylation site.

16. A pseudovirion comprising a retroviral Gag protein and a fusion partner, wherein the fusion partner is present in a Gag-fs-fusion partner fusion protein.

17. The pseudovirion of claim 16, wherein the fusion partner is derived from a protein selected from the group consisting of an interleukin, TNF, GM/CSF, a nonretroviral viral antigen, a cancer antigen and a molecule involved in signal transduction.

18. The pseudovirion of claim 17, wherein the fusion partner is derived from a protein selected from the group consisting of IL-1, IL-2, IL-4, IL-6, MART-1, gp 100, tyrosinase, bcl-1, bcl-2, c-myc, int-2, hst-1, ras, p53, prostate-specific membrane antigen, papilloma virus protein L1, protein kinase C., and G proteins.

19. The pseudovirion of claim 16, wherein the fusion partner is derived from a retroviral Env protein.

20. The pseudovirion of claim 16, wherein the pseudovirion is noninfectious.

21. The pseudovirion of claim 19, wherein the Env protein domain is present primarily in the interior of the pseudovirion.

22. The pseudovirion of claim 19, wherein the Gag-fs-Env fusion protein is the Gag-fs-SU fusion protein, or a conservative modification thereof.

23. The pseudovirion of claim 19, wherein the Gag-fs-Env fusion protein is the Gag-fs-SU fusion protein.

24. The pseudovirion of claim 19, wherein the Env fusion partner is present in a Gag-fs-Env fusion protein, and wherein Gag protein is separately present in the fusion protein and as an independent protein.

25. The pseudovirion of claim 19, wherein the pseudovirion is made by transducing an insect cell with a baculovirus vector, which vector encodes a Gag-fs-Env protein.

26. The pseudovirion of claim 19, wherein the pseudovirion, when administered as an **immunogenic** composition in mice, elicits a **CTL** response against Env, but does not elicit antibodies which recognize Env.

27. An **immunogenic** composition comprising a pseudovirion comprising a retroviral Gag protein and a retroviral fusion partner, wherein the fusion partner is present in a Gag-fs-fusion partner fusion protein and wherein the fusion partner is derived from a retroviral Env protein.

28. The **immunogenic** composition of claim 27, wherein the **immunogenic** composition, when administered to mice, elicits a **CTL** response against Env, but does not elicit antibodies against Env.

29. A particulate **vaccine** comprising a pseudovirion comprising a retroviral Gag protein and a retroviral fusion partner, wherein the fusion partner is present in a Gag-fs-fusion partner fusion protein and wherein the fusion partner is derived from a retroviral Env protein.

30. The particulate **vaccine** of claim 29, wherein the **vaccine**, when administered to mice, elicits a **CTL** response against Env, but does not

elicit antibodies against Env.

31. A fusion protein comprising a retroviral Gag sequence, a translation reading frame switching sequence and a fusion partner.

32. The fusion protein of claim 31, wherein the fusion partner is a retroviral Env amino acid subsequence.

33. The fusion protein of claim 31, wherein the fusogenic partner is selected from the group consisting of Env, an interleukin, TNF, GM/CSF, a nonretroviral viral antigen, a cancer antigen and a molecule involved in signal transduction.

34. The fusion protein of claim 31, wherein the fusogenic partner is selected from the group consisting of IL-1, IL-2, IL-4, IL-6, MART-1, gp 100, tyrosinase, bcl-1, bcl-2, c-myc, int-2, hst-1, ras, p53, prostate-specific membrane antigen, papilloma virus protein L1, protein kinase C. and G proteins.

35. The fusion protein of claim 32, wherein the Env amino acid subsequence comprises the carboxyl 65% of a retroviral Env protein.

36. The fusion protein of claim 32, wherein the Env amino acid subsequence is derived from **HIV**.

37. The fusion protein of claim 31, wherein the translation reading frame switching sequence comprises sequences derived from the N-terminus of a retroviral Pol protein.

38. A method of making a pseudovirion comprising expressing a **nucleic acid** encoding a Gag-fs-fusion partner fusion protein in a cell, wherein the cell translates the **nucleic acid** into a first protein comprising a Gag sequence, and a second protein comprising a gag sequence and a fusogenic partner.

39. The method of claim 38, wherein the fusogenic partner comprises an env sequence.

40. The method of claim 38, wherein the cell is an insect cell.

41. The method of claim 38, wherein the method further comprises the step of purifying the pseudovirion.

42. A pseudovirion comprising a retroviral Gag protein and a fusion partner, wherein the fusion partner is present in Gag-fs-fusion partner fusion protein and wherein the fusion partner is derived from retroviral Env protein.

43. A fusion protein comprising a retroviral Gag sequence, a translation reading frame switching sequence and a retroviral Env amino acid subsequence.

L27 ANSWER 21 OF 33 USPATFULL on STN
2000:4680 Crossless retroviral vectors.
Respess, James G., San Diego, CA, United States
DePolo, Nicholas J., Solana Beach, CA, United States
Chada, Sunil, Missouri City, TX, United States
Sauter, Sybille, Del Mar, CA, United States
Bodner, Mordechai, San Diego, CA, United States
Driver, David A., San Diego, CA, United States
Chiron Corporation, Emeryville, CA, United States (U.S. corporation)
US 6013517 20000111
APPLICATION: US 1997-850961 19970505 (8) <--
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Retroviral vector constructs are described which have a 5' LTR, a tRNA binding site, a packaging signal, one or more heterologous sequences, an origin of second strand synthesis and a 3' LTR, wherein the vector construct lacks retroviral gag/pol or env coding sequences. In addition, gag/pol, and env expression-cassettes are described wherein the expression cassettes lack a consecutive sequence of more than 8 nucleotides in common. The above-described retroviral vector constructs, gag/pol and env expression cassettes may be utilized to construct producer cell lines which preclude the formation of replication competent virus.

CLM What is claimed is:

1. A retroviral vector construct comprising a 5' LTR, a tRNA binding site, a packaging signal, an origin of second strand **DNA** synthesis and a 3' LTR, wherein said vector construct contains gag/pol coding sequences which have been modified to contain two or more stop codons.

2. The retroviral vector construct according to claim 1 wherein said vector construct lacks an extended packaging signal.

3. The retroviral vector construct according to claim 1 wherein said construct lacks a retroviral **nucleic acid** sequence upstream of said 5' LTR.

4. The retroviral vector construct according to claim 1 wherein said construct lacks an env coding and/or untranslated env sequence upstream of said 3' LTR.

5. The retroviral vector construct according to claim 1 wherein said construct lacks a retroviral packaging signal sequence downstream of said 3' LTR.

6. The retroviral vector construct according to claim 1 wherein said retroviral vector is constructed from a retrovirus selected from the group consisting of amphotropic, ecotropic, xenotropic and polytropic viruses.

7. The retroviral vector construct according to claim 1 wherein said retroviral vector is constructed from a Murine Leukemia Virus.

8. The retroviral vector construct according to claim 1, further comprising a heterologous sequence.

9. The retroviral vector construct according to claim 3 wherein said construct lacks an env coding sequence upstream of said 5' LTR.

10. The retroviral vector construct according to claim 8 wherein said heterologous sequence is a gene encoding a **cytotoxic** protein.

11. The retroviral vector construct according to claim 8 wherein said heterologous sequence is an antisense sequence.

12. The retroviral vector construct according to claim 8 wherein said heterologous sequence encodes an immune accessory molecule.

13. The retroviral vector construct according to claim 8 wherein said heterologous sequence encodes a gene product that activates a compound with little or no cytotoxicity into a toxic product.

14. The retroviral vector construct according to claim 8 wherein said heterologous sequence is a ribozyme.

15. The retroviral vector construct according to claim 8 wherein said heterologous sequence is a replacement gene.

16. The retroviral vector construct according to claim 8 wherein said heterologous sequence encodes an **immunogenic** portion of a virus

selected from the group consisting of HBV, HCV, HPV, EBV, FeLV, FIV, and **HIV**.

17. The retroviral vector construct according to claim 10 wherein said **cytotoxic** protein is selected from the group consisting of ricin, abrin, diphtheria toxin, cholera toxin, gelonin, pokeweed, antiviral protein, tritin, Shigella toxin, and Pseudomonas exotoxin A.

18. The retroviral vector construct according to claim 12 wherein said immune accessory molecule is selected from the group consisting of IL-1, IL-2, IL-3, IL-4, IL-5, IL,-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13 and IL-15.

19. The retroviral vector construct according to claim 12 wherein said immune accessory molecule is selected from the group consisting of ICAM-1, ICAM-2, b-microglobin, LFA3, HLA class I and HLA class II molecules.

20. The retroviral vector construct according to claim 13 wherein said gene product is selected from the group consisting of HSVTK, VZVTK and cytosine deaminase.

21. The retroviral vector construct according to claim 15 wherein said replacement gene encodes a protein selected from the group consisting of Factor VIII, ADA, HPRT, CF and the LDL Receptor.

22. A producer cell line, comprising a gag/pol expression cassette, an env expression cassette and a retroviral vector construct, wherein the 3' terminal end of a gag/pol gene encoded within said gag/pol expression cassette lacks homology with the 5' terminal end of an env gene encoded within said env expression cassette, and wherein the 3' terminal end of said env gene lacks homology with said retroviral vector construct, with the proviso that said retroviral vector construct overlaps with at least 4 nucleotides of the 5' terminal end of said gag/pol gene encoded within said gag/pol expression cassette.

23. The producer cell line according to claim 22 wherein said retroviral vector construct is a retroviral vector construct according to any one of claims 1 to 21.

24. The producer cell line according to claim 22 wherein said gag/pol expression cassette comprises a promoter operably linked to a gag/pol gene, and a polyadenylation sequence, wherein the 3' terminal end of said gag/pol gene has been deleted without affecting the biological activity of integrase.

25. The producer cell line according to claim 22 wherein said env expression cassette comprises a promoter operably linked to an env gene, and a polyadenylation sequence, wherein no more than 6 consecutive retroviral nucleotides are included upstream of said env gene.

26. The producer cell line according to claim 22 wherein said env expression cassette comprises a promoter operably linked to an env gene, and a polyadenylation sequence, wherein said env expression cassette does not contain a consecutive sequence of more than 8 nucleotides which are found in a gag/pol gene.

27. The producer cell line according to claim 22 wherein said env expression cassette comprises a promoter operably linked to an env gene, and a polyadenylation sequence, wherein a 3' terminal end of said env gene has been deleted without effecting the biological activity of env.

28. The producer cell line according to claim 24 wherein said 3' terminal end has been deleted upstream of nucleotide 5751 of SEQ ID NO: 1.

29. The producer cell line according to claim 24 wherein said promoter is a heterologous promoter.

30. The producer cell line according to claim 24 wherein said promoter is selected from the group consisting of CMV IE, the HSVTK promoter, RSV promoter, Adenovirus major-later promoter and the SV40 promoter.

31. The producer cell line according to claim 24 wherein said polyadenylation sequence is a heterologous polyadenylation sequence.

32. The producer cell line according to claim 31 wherein said heterologous polyadenylation sequence is selected from the group consisting of the SV40 late poly A signal, the SV40 early poly A signal and a bovine growth hormone poly A signal.

33. The producer cell line according to claim 27 wherein a 3' terminal end of said env gene has been deleted such that a complete R peptide is not produced by said expression cassette.

34. The producer cell line according to claim 27 wherein said promoter is a heterologous promoter.

35. The producer cell line according to claim 27 wherein said polyadenylation sequence is a heterologous polyadenylation sequence.

36. The producer cell line according to claim 33 wherein said env gene is derived from a type C retrovirus, and wherein the 3' terminal end has been deleted such that said env gene includes less than 18 nucleic acids which encode said R peptide.

37. The producer cell line according to claim 34 wherein said heterologous promoter is selected from the group consisting of CMV IE, the HSVTK promoter, RSV promoter, Adenovirus major-later promoter and the SV40 promoter.

38. The producer cell line according to claim 35 wherein said heterologous polyadenylation is selected from the group consisting of the SV40 late poly A signal, the SV40 early poly A signal and a bovine growth hormone polyadenylation sequence.

L27 ANSWER 22 OF 33 USPATFULL on STN
1999:166852 Redirection of cellular immunity by protein tyrosine kinase chimeras.
Seed, Brian, Boston, MA, United States
Romeo, Charles, Belmont, MA, United States
Kolanus, Waldemar, Watertown, MA, United States
The Massachussetts General Hospital, Boston, MA, United States (U.S. corporation)
US 6004811 19991221 <--
APPLICATION: US 1995-394912 19950224 (8)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Disclosed is a method of directing a cellular response in a mammal by expressing in a cell of the mammal a chimeric receptor which causes the cells to specifically recognize and destroy an infective agent, a cell infected with an infective agent, a tumor or cancerous cell, or an autoimmune-generated cell. The chimeric receptor includes an extracellular portion which is capable of specifically recognizing and binding the target cell or target infective agent, and (b) an intracellular portion of a protein-tyrosine kinase which is capable of signalling the therapeutic cell to destroy a receptor-bound target cell or a receptor-bound target infective agent. Also disclosed are calls which express the chimeric receptors and DNA encoding the chimeric receptors.
CLM What is claimed is:

1. An isolated **cytotoxic** T cell which expresses a membrane bound chimeric receptor, said chimeric receptor comprising: (a) an intracellular portion of a Syk protein-tyrosine kinase which signals said **cytotoxic** T-cell to destroy a receptor-bound target cell; (b) a transmembrane domain; and (c) an extracellular portion of an immunoglobulin superfamily protein which specifically recognizes and binds said target cell; and wherein said chimeric receptor signals said **cytotoxic** T-cell to destroy said target cell.

2. The **cytotoxic** T cell of claim 1, wherein said intracellular portion includes human Syk amino acids 336-628 g or porcine Syk amino acids 338-630.

3. The **cytotoxic** T-cell of claim 1, wherein said target cell is infected with an immunodeficiency virus.

4. The **cytotoxic** T-cell of claim 3, wherein said extracellular portion comprises an **HIV** envelope-binding portion of CD4.

5. An isolated **cytotoxic** T-cell which expresses at least two different membrane-bound chimeric receptors, the first of said chimeric receptors comprising: (a) an intracellular portion of a ZAP-70 protein tyrosine-kinase; (b) a transmembrane domain; and (c) an extracellular portion of an immunoglobulin superfamily protein which specifically recognizes and binds a target cell; and the second of said chimeric receptors comprising (a) an intracellular portion of a Src family protein-tyrosine kinase; (b) a transmembrane domain; and (c) an extracellular portion of an immunoglobulin superfamily protein which specifically recognizes and binds said target cell; and wherein said ZAP-70 and said Src family protein-tyrosine kinases together signal said **cytotoxic** T-cell to destroy said target cell when said extracellular portions of said first and said second chimeric receptors are bound to said target cell.

6. The **cytotoxic** T-cell of claim 5, wherein said Src family protein-tyrosine kinase is Fyn.

7. The **cytotoxic** T-cell of claim 5, wherein said Src family protein-tyrosine kinase is Lck.

8. The **cytotoxic** T cell of claim 5, wherein said ZAP-70 portion includes human ZAP-70 Tyr 369.

9. The **cytotoxic** T-cell of claim 5, wherein said target cell is infected with an immunodeficiency virus.

10. The **cytotoxic** T cell of claim 9, wherein at least one said extracellular portion comprises an **HIV** envelope-binding portion of CD4.

11. The **cytotoxic** T-cell of claims 1 or 5, wherein said signaling is MHC-independent.

12. The **cytotoxic** T cell of claims 1 or 5, wherein said extracellular portion comprises the ligand-binding portion of a receptor, the receptor-binding portion of a ligand, or the antigen-binding portion of an antibody.

13. **DNA** encoding a chimeric receptor which comprises (a) an intracellular portion of a Syk protein-tyrosine kinase; (b) a transmembrane domain; and (c) an extracellular portion of an immunoglobulin superfamily protein.

14. A vector comprising the **DNA** of claim 13.

15. The **DNA** of claim 13, wherein said intracellular portion includes human Syk amino acids 336-628 or porcine Syk amino acids 338-630.

16. The **DNA** of claim 13, wherein said extracellular portion comprises an **HIV**-envelope binding portion of CD4.

17. The **DNA** of claim 13, wherein said extracellular portion comprises the ligand-binding portion of a receptor, the receptor-binding portion of a ligand, or the antigen-binding portion of an antibody.

18. The **cytotoxic** T cell of claim 1, wherein said Syk protein-tyrosine kinase is a human Syk protein-tyrosine kinase.

19. The **cytotoxic** T cell of claim 5, wherein said ZAP-70 protein-tyrosine kinase is a human ZAP-70 protein-tyrosine kinase.

20. The **cytotoxic** T cell of claim 5, wherein said Src protein-tyrosine kinase is a human Src protein-tyrosine kinase.

21. The **cytotoxic** T cell of claims 1 or 5, wherein said immunoglobulin superfamily protein is CD16.

22. The **DNA** of claim 13, wherein said Syk protein-tyrosine kinase is a human Syk protein-tyrosine kinase.

23. The **DNA** of claim 13, wherein said immunoglobulin superfamily protein is CD16.

L27 ANSWER 23 OF 33 USPATFULL on STN
1999:125062 Method of eliminating inhibitory/ instability regions of mRNA.
Pavlakis, George N., Rockville, MD, United States
Felber, Barbara K., Rockville, MD, United States
The United States of America as represented by the Department of Health and Human Services, Washington, DC, United States (U.S. government)
US 5965726 19991012
APPLICATION: US 1997-850049 19970502 (8) <--
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method of locating an inhibitory/instability sequence or sequences within the coding region of an mRNA and modifying the gene encoding that mRNA to remove these inhibitory/instability sequences by making clustered nucleotide substitutions without altering the coding capacity of the gene is disclosed. Constructs containing these mutated genes and host cells containing these constructs are also disclosed. The method and constructs are exemplified by the mutation of a **Human Immunodeficiency Virus**-1 Rev-dependent gag gene to a Rev-independent gag gene. Constructs useful in locating inhibitory/instability sequences within either the coding region or the 3' untranslated region of an mRNA are also disclosed. The exemplified constructs of the invention may also be useful in **HIV**-1 immunotherapy and immunoprophylaxis.

CLM What is claimed is:

1. A composition comprising a **nucleic acid** construct and a carrier, wherein said **nucleic acid** construct comprises a **nucleic acid** sequence capable of producing **HIV** gag protein in the absence of **HIV** Rev protein, and wherein said **nucleic acid** sequence comprises multiple point mutations which decrease the effect of an inhibitory/instability sequence which is present in the corresponding **nucleic acid** sequence of the native **HIV** gag gene.

2. A composition of claim 1 wherein said **nucleic acid** construct comprises multiple point mutations between nucleotides corresponding to nucleotides 402 and 452, 536 and 583, 585 and 634, and 654 and 703 of the nucleotide sequence of the **HIV**-1 molecular clone pHXB2.

3. A composition of claim 2 wherein said **nucleic acid** construct comprises the following nucleotide sequences:
CCAGGGGGAAAGAAGAAGTACAAGCTAAAGCACATCGTATGGGCAAGCAGG (SEQ ID NO: 6) at

nucleotides corresponding to nucleotides 402-452 of the **HIV**-1 molecular clone pHXB2; CCTTCAGACAGGATCAGAGGAGCTTCGATCACTATACAACACAGTAGC (SEQ ID NO: 7) at nucleotides corresponding to nucleotides 536-583 of the **HIV**-1 molecular clone pHXB2; ACCCTCTATTGTGTGCACCAGCGGATCGAGATCAAGG ACACCAAGGAAGC (SEQ ID NO: 8) at nucleotides corresponding to nucleotides 585-634 of the **HIV**-1 molecular clone pHXB2; and GAGCAAAACAAGTCCAAGAAGAAGGCCCAGCAGGCAGCAGCTGACACAGG (SEQ ID NO: 9) at nucleotides corresponding to nucleotides 654-703 of the **HIV**-1 molecular clone pHXB2.

4. A composition of claim 1 wherein said **nucleic acid** construct comprises multiple point mutations between nucleotides corresponding to nucleotides 402 and 452, 536 and 583, 585 and 634, 654 and 703, 871 and 915, 1105 and 1139, 1140 and 1175, and 1321 and 1364 of the nucleotide sequence of the **HIV**-1 molecular clone pHXB2.

5. A composition of claim 4 wherein said **nucleic acid** construct comprises the following nucleotide sequences: CCAGGGGGAAAGAAGAAGTACAAGCTAAAGCACATCGTATGGGCAAGCAGG (SEQ ID NO: 6) at nucleotides corresponding to nucleotides 402-452 of the **HIV**-1 molecular clone pHXB2; CCTTCAGACAGGATCAGAGGAGCTTCGATCACTATACAACACAGTAGC (SEQ ID NO: 7) at nucleotides corresponding to nucleotides 536-583 of the **HIV**-1 molecular clone pHXB2; ACCCTCTATTGTGTGCACCAGCGGATCGAGATCAAGG ACACCAAGGAAGC (SEQ ID NO: 8) at nucleotides corresponding to nucleotides 585-634 of the **HIV**-1 molecular clone pHXB2; GAGCAAAACAAGTCCAAGAAGAAGGCCCAGCAGGCAGCAGCTGACACAGG (SEQ ID NO: 9) at nucleotides corresponding to nucleotides 654-703 of the **HIV**-1 molecular clone pHXB2; CCACCCCACAGGACCTGAACACGATGTTGAACACCGTGGGGGGAC (SEQ ID NO: 25) at nucleotides corresponding to nucleotides 871-915 of the **HIV**-1 molecular clone pHXB2; CAGTAGGAGAGATCTACAAGAGGTGGATAATCCTG (SEQ ID NO: 27) at nucleotides corresponding to nucleotides 1105-1139 of the **HIV**-1 molecular clone pHXB2; GGATTGAACAAGATCGTGAGGATGTATAGCCCTACC (SEQ ID NO: 29) at nucleotides corresponding to nucleotides 1140-1175 of the **HIV**-1 molecular clone pHXB2; and ATTGTAAGACCATCCTGAAGGCTCTCGGCCCAG CGGCTACACTA (SEQ ID NO: 33) at nucleotides corresponding to nucleotides 1321-1364 of the **HIV**-1 molecular clone pHXB2.

6. The construct of claim 5 wherein said **nucleic acid** construct comprises the nucleotide sequence:

ATG GGT GCG AGA GCG TCA GTA TTA AGC GGG GGA GAA TTA GAT
CGA TGG GAA AAA ATT CGG TTA AGG CCA GGG GGA AAG AAG AAG TAC AAG
CTA AAG CAC ATC GTA TGG GCA AGC AGG GAG CTA GAA CGA TTC GCA GTT
AAT CCT GGC CTG TTA GAA ACA TCA GAA GGC TGT AGA CAA ATA CTG GGA
CAG CTA CAA CCA TCC CTT CAG ACA GGA TCA GAG GAG CTT CGA TCA CTA
TAC AAC ACA GTA GCA ACC CTC TAT TGT GTG CAC CAG CGG ATC GAG ATC
AAG GAC ACC AAG GAA GCT TTA GAC AAG ATA GAG GAA GAG CAA AAC AAG
TCC AAG AAG AAG GCC CAG CAG GCA GCA GCT GAC ACA GGA CAC AGC AAT
CAG GTC AGC CAA AAT TAC CCT ATA GTG CAG AAC ATC CAG GGG CAA ATG
GTA CAT CAG GCC ATA TCA CCT AGA ACT TTA AAT GCA TGG GTA AAA GTA
GTA GAA GAG AAG GCT TTC AGC CCA GAA GTG ATA CCC ATG TTT TCA GCA
TTA TCA GAA GGA GCC ACC CCA CAG GAC CTG AAC ACG ATG TTG AAC ACC
GTG GGG GGA CAT CAA GCA GCC ATG CAA ATG TTA AAA GAG ACC ATC AAT
GAG GAA GCT GCA GAA TGG GAT AGA GTG CAT CCA GTG CAT GCA GGG CCT
ATT GCA CCA GGC CAG ATG AGA GAA CCA AGG GGA AGT GAC ATA GCA GGA
ACT ACT AGT ACC CTT CAG GAA CAA ATA GGA TGG ATG ACA AAT AAT CCA
CCT ATC CCA GTA GGA GAG ATC TAC AAG AGG TGG ATA ATC CTG GGA TTG
AAC AAG ATC GTG AGG ATG TAT AGC CCT ACC AGC ATT CTG GAC ATA AGA
CAA GGA CCA AAG GAA CCC TTT AGA GAC TAT GTA GAC CGG TTC TAT AAA
ACT CTA AGA GCT GAG CAA GCT TCA CAG GAG GTA AAA AAT TGG ATG ACA
GAA ACC TTG TTG GTC CAA AAT GCG AAC CCA GAT TGT AAG ACC ATC CTG
AAG GCT CTC GGC CCA GCG GCT ACA CTA GAA GAA ATG ATG ACA GCA TGT
CAG GGA GTA GGA GGA CCC GGC CAT AAG GCA AGA GTT TTG (nucleotides 729 to 1817 of
Sequence I.D. No. 129).

7. A composition of claim 1 wherein said **nucleic acid** construct comprises multiple point mutations between nucleotides corresponding to nucleotides 402 and 452, 536 and 583, 585 and 634, 654 and 703, 871 and 915, 1105 and 1139, 1140 and 1175, 1321 and 1364, 1416 and 1466, 1470 and 1520, 1527 and 1574, and 1823 and 1879 of the nucleotide sequence of the **HIV**-1 molecular clone pHXB2.

8. A composition of claim 7 wherein said **nucleic acid** construct comprises the following nucleotide sequences: AGAGTTTTGGCCGAGGCGATGAGCCAGGTGACGAACTCGGCGACCATAATG (SEQ ID NO: 35) at nucleotides corresponding to nucleotides 1416-1466 of the **HIV**-1 molecular clone pHXB2; CAGAGAGGCAACTTCCGGAACCAGCGGAAGATCGTCAAGTGTTTCAATT GT (SEQ ID NO: 37) at nucleotides corresponding to nucleotides 1470-1520 of the **HIV**-1 molecular clone pHXB2; GAAGGGCACACCGCCAGGAACTGCCGGGCCCCCC GGAAGAAGGGCTGT (SEQ ID NO: 39) at nucleotides corresponding to nucleotides 1527-1574 of the **HIV**-1 molecular clone pHXB2; and CCCCTCGTCACAGTAAGGATCGGGGGCAACTCAAGGAAGCGCTGCTCGATA CAGGAG (SEQ ID NO: 43) at nucleotides corresponding to nucleotides 1823-1879 of the **HIV**-1 molecular clone pHXB2.

9. A composition of claim 1 wherein said **nucleic acid** construct comprises multiple point mutations between nucleotides corresponding to nucleotides 402 and 452, and nucleotides 536-583, of the nucleotide sequence of the **HIV**-1 molecular clone pHXB2.

10. A composition of claim 9 wherein said **nucleic acid** construct comprises the following nucleotide sequences: CCAGGGGGAAAGAAGAAGTACAAGCTAAAGCACATCGTATGGGCAAGCAGG (SEQ ID NO: 6) at nucleotides corresponding to nucleotides 402-452 of the **HIV**-1 molecular clone pHXB2; and CCTTCAGACAGGATCAGAGGAGCTTCGATCACTATACAACACAGT AGC (SEQ ID NO: 7) at nucleotides corresponding to nucleotides 536-583 of the **HIV**-1 molecular clone pHXB2.

11. A composition of claim 1 wherein said **nucleic acid** construct comprises multiple point mutations between nucleotides corresponding to nucleotides 402 and 452, and nucleotides 585 and 634, of the nucleotide sequence of the **HIV**-1 molecular clone pHXB2.

12. A composition of claim 11 wherein said **nucleic acid** construct comprises the following nucleotide sequences: CCAGGGGGAAAGAAGAAGTACAAGCTAAAGCACATCGTATGGGCAAGCAGG (SEQ ID NO: 6) at nucleotides corresponding to nucleotides 402-452 of the **HIV**-1 molecular clone pHXB2; and ACCCTCTATTGTGTGCACCAGCGGATCGAGATCAAGGACACCAAG GAAGC (SEQ ID NO: 8) at nucleotides corresponding to nucleotides 585-634 of the **HIV**-1 molecular clone pHXB2.

13. A composition of claim 1 wherein said **nucleic acid** construct comprises multiple point mutations between nucleotides corresponding to nucleotides 402 and 452, and nucleotides 654 and 703, of the nucleotide sequence of the **HIV**-1 molecular clone pHXB2.

14. A composition of claim 13 wherein said **nucleic acid** construct comprises the following nucleotide sequences: CCAGGGGGAAAGAAGAAGTACAAGCT AAAGCACATCGTATGGGCAAGCAGG (SEQ ID NO: 6) at nucleotides corresponding to nucleotides 402-452 of the **HIV**-1 molecular clone pHXB2; and GAGCAAAACAAGTCCAAGAAGAAGGCCCAGCAGGCAGCAGCTGACACAGG (SEQ ID NO: 9) at nucleotides corresponding to nucleotides 654-703 of the **HIV**-1 molecular clone pHXB2.

15. A composition of claim 1 wherein said **nucleic acid** construct comprises multiple point mutations between nucleotides corresponding to nucleotides 536 and 583, and nucleotides 585 and 634, of the nucleotide sequence of the **HIV**-1 molecular clone pHXB2.

16. A composition of claim 15 wherein said **nucleic acid** construct comprises the following nucleotide sequences: CCTTCAGACAGGATCAGAGGAGCTTCGATCACTATACAACACAGTAGC (SEQ ID NO: 7) at nucleotides corresponding to nucleotides 536-583 of the **HIV**-1 molecular clone pHXB2; and ACCCTCTATTGTGTGCACCAGCGGATCGAGATCAAGGACACCAAG GAAGC (SEQ ID NO: 8) at nucleotides corresponding to nucleotides 585-634 of the **HIV**-1 molecular clone pHXB2.

17. A composition of claim 1 wherein said **nucleic acid** construct comprises multiple point mutations between nucleotides corresponding to nucleotides 536 and 583, and nucleotides 654 and 703, of the nucleotide sequence of the **HIV**-1 molecular clone pHXB2.

18. A composition of claim 17 wherein said **nucleic acid** construct comprises the following nucleotide sequences: CCTTCAGACAGGATCAGAGGAGCTTCGATCACTATACAACACAGTAGC (SEQ ID NO: 7) at nucleotides corresponding to nucleotides 536-583 of the **HIV**-1 molecular clone pHXB2; and GAGCAAAACAAGTCCAAGAAGAAGGCCCAGCAGGCAGCAGCTGAC ACAGG (SEQ ID NO: 9) at nucleotides corresponding to nucleotides 654-703 of the **HIV**-1 molecular clone pHXB2.

19. A composition of claim 1 wherein said **nucleic acid** construct comprises multiple point mutations between nucleotides corresponding to nucleotides 585 and 634, and nucleotides 654 and 703, of the nucleotide sequence of the **HIV**-1 molecular clone pHXB2.

20. A composition of claim 19 wherein said **nucleic acid** construct comprises the following nucleotide sequences: ACCCTCTATTGTGTGCACCAGCGGATCGAGATCAAGGACACCAAGGAAGC (SEQ ID NO: 8) at nucleotides corresponding to nucleotides 585-634 of the **HIV**-1 molecular clone pHXB2; and GAGCAAAACAAGTCCAAGAAGAAGGCCCAGCAGGCAGCAGCTGAC ACAGG (SEQ ID NO: 9) at nucleotides corresponding to nucleotides 654-703 of the **HIV**-1 molecular clone pHXB2.

21. A composition comprising a **nucleic acid** construct and a carrier, wherein said **nucleic acid** construct comprises a **nucleic acid** sequence capable of producing **HIV** env protein in the absence of **HIV** Rev protein, and wherein said **nucleic acid** sequence comprises multiple point mutations which decrease the effect of an inhibitory/instability sequence which is present in the corresponding **nucleic acid** sequence of the native **HIV** env gene.

22. A composition of claim 21 wherein said **nucleic acid** construct comprises multiple point mutations between nucleotides corresponding to nucleotides 8194 and 8261, 8262 and 8323, 8335 and 8392, 8393 and 8450, 8451 and 8512, and 8513 and 8572 of the nucleotide sequence of the **HIV**-1 molecular clone pHXB2.

23. A composition according to claim 22 wherein said **nucleic acid** construct comprises the following sequence GAATAGTGCTGTTAACCTCCTGAACGCTA CCGCTATCGCCGTGGCGGAAGGAA CCGACAGGGTTATAG (SEQ ID NO: 10) at nucleotides corresponding to nucleotides 8194-8261 of the **HIV**-1 molecular clone pHXB2; AAGTATTACAAGCCGCCTACCGCGCCATCAGACATATCCCCCGCCGCATCCGC CAGGGCTTG (SEQ ID NO: 11) at nucleotides corresponding to nucleotides 8262-8323 of the **HIV**-1 molecular clone pHXB2; GCTATAAGATGGGCGGTAAATGGAGCAAGTCCTCCGT CATCGGCTGGCCTGCT GTAAG (SEQ ID NO: 12) at nucleotides corresponding to nucleotides 8335-8392 of the **HIV**-1 molecular clone pHXB2; GGAAAGAATGCGCAGGGCCGAACCCGCCGCCGACGGAGTTGGCGCCGTATCT CGAGAC (SEQ ID NO: 13) at nucleotides corresponding to nucleotides 8393-8450 of the **HIV**-1 molecular clone pHXB2; CTAGAAAAACACGGCGCCATTACCTCCTCTAACACCGCCGCCAATAACG CCGC TTGTGCCTG (SEQ ID NO: 14) at nucleotides corresponding to nucleotides 8451-8512 of the **HIV**-1 molecular clone pHXB2; and GCTAGAAGCACAGGAAGAAGAGGAAGTCGGCTTCCCCGTTACCCCTCAGGTA CCTTTAAG (SEQ ID NO: 15) at nucleotides corresponding to nucleotides 8513-8572 of the **HIV**-1 molecular clone pHXB2.

24. A composition comprising a **nucleic acid** construct and a carrier, wherein said **nucleic acid** construct comprises a **nucleic acid** sequence capable of producing **HIV** pol protein in the absence of **HIV** Rev protein, and wherein said **nucleic acid** sequence comprises multiple point mutations which decrease the effect of an inhibitory/instability sequence which is present in the corresponding **nucleic acid** sequence of the native **HIV** pol gene.

25. A composition according to any one of claims 1 to 20, wherein said composition is useful for inducing antibodies which react with **HIV** gag protein in a mammal; said carrier is a pharmaceutically acceptable carrier for administering to a mammal; and said **nucleic acid** construct is present in an amount which is capable of expressing **HIV** gag protein in an amount which is effective to induce said antibodies in said mammal.

26. A composition according to any one of claims 1 to 20, wherein said composition is useful for inducing **cytotoxic** T lymphocytes in a mammal; said carrier is a pharmaceutically acceptable carrier; and said **nucleic acid** construct is present in an amount which is capable of expressing **HIV** gag protein in an amount which is effective to induce said **cytotoxic** T lymphocytes in said mammal.

27. A composition according to any one of claims 21 to 23, wherein said composition is useful for inducing antibodies which react with **HIV** env protein in a mammal; said carrier is a pharmaceutically acceptable carrier; and said **nucleic acid** construct is present in an amount which is capable of expressing **HIV** env protein in an amount which is effective to induce said antibodies in said mammal.

28. A composition according to any one of claims 21 to 23, wherein said composition is useful for inducing **cytotoxic** T lymphocytes in a mammal, said carrier is a pharmaceutically acceptable carrier; and said **nucleic acid** construct is present in an amount which is capable of expressing **HIV** env protein in an amount which is effective to induce said **cytotoxic** T lymphocytes in said mammal.

29. A composition according to claim 24, wherein said composition is useful for inducing antibodies which react with **HIV** pol protein in a mammal; said carrier is a pharmaceutically acceptable carrier; and said **nucleic acid** construct is present in an amount which is capable of expressing **HIV** pol protein in an amount which is effective to induce said antibodies in said mammal.

30. A composition according claim 24, wherein said composition is useful for inducing **cytotoxic** T lymphocytes in a mammal; said carrier is a pharmaceutically acceptable carrier; and said **nucleic acid** construct is present in an amount which is capable of expressing **HIV** pol protein in an amount which is effective to induce said **cytotoxic** T lymphocytes in said mammal.

31. A method for inducing antibodies in a mammal comprising administering to a mammal a composition of claim 25.

32. A method for inducing **cytotoxic** T lymphocytes in a mammal comprising administering to a mammal a composition of claim 26.

33. A method for inducing antibodies in a mammal comprising administering to a mammal a composition of claim 27.

34. A method for inducing **cytotoxic** T lymphocytes in a mammal comprising administering to a mammal a composition of claim 28.

35. A method for inducing antibodies in a mammal comprising administering to a mammal a composition of claim 29.

36. A method for inducing **cytotoxic** T lymphocytes in a mammal comprising administering to a mammal a composition of claim 30.

L27 ANSWER 24 OF 33 USPATFULL on STN
1999:117339 Chimeric antiviral agents comprising Rev binding nucleic acids and trans-acting ribozymes, and molecules encoding them.
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Yu, Mang, San Diego, CA, United States
Yamada, Osamu, Kobe, Japan
The Regents of the University of California, Oakland, CA, United States (U.S. corporation)
US 5958768 19990928
APPLICATION: US 1996-697324 19960823 (8) <--
PRIORITY: US 1995-2793P 19950825 (60)
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Methods and compositions for the treatment and diagnosis of infections of Rev-binding primate lentiviruses are provided. These methods and compositions utilize the ability of Rev binding nucleic acids such as the SLII sequence from the **HIV**-1 Rev response element (RRE) to target therapeutic agents to the same sub-cellular location as primate lentiviruses which contain RRE sequences. In particular, the invention provides trans-acting ribozymes comprising Rev-binding nucleic acids less toxic than a full-length RRE, and molecules encoding them. The use of the compositions of the invention as components of diagnostic assays, as prophylactic reagents, and in vectors is also described.

CLM What is claimed is:

1. A molecule selected from a trans-active ribozyme which hybrdizes to a **nucleic acid** of a Rev-binding primate lentivirus, wherein said trans-active ribozyme comprises a Rev-binding **nucleic acid** which is less **cytotoxic** than a full-length Rev response element, and a molecule which encodes a trans-active ribozyme which hybridizes to a **nucleic acid** of a Rev-binding primate lentivirus, wherein said trans-active ribozyme comprises a Rev-binding **nucleic acid** which is less **cytotoxic** than a full-length Rev response element.

2. The molecule of claim 1, which is a trans-active ribozyme, wherein said trans-active ribozyme comprises a Rev-binding **nucleic acid** which is less **cytotoxic** than a full-length Rev response element.

3. The molecule of claim 2, wherein said Rev-binding **nucleic acid** is an SL II **nucleic acid**.

4. The molecule of claim 2 wherein said SL II **nucleic acid** comprises the **nucleic acid** of SEQ ID NO: 1.

5. The molecule of claim 2, wherein said ribozyme is a hairpin ribozyme.

6. The molecule of claim 2, wherein said ribozyme comprises a plurality of Rev-binding nucleic acids.

7. The molecule of claim 2, wherein said ribozyme comprises an SL II **nucleic acid** at the 3' terminus of the ribozyme and a second SL II **nucleic acid** at the 5' terminus of the ribozyme.

8. The molecule of claim 2 wherein said ribozyme has a sequence selected from the group of SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, and SEQ ID NO:7.

9. The molecule of claim 2, wherein said ribozyme cleaves an **HIV**-1 **nucleic acid** in a cell culture.

10. The molecule of claim 1, which encodes a trans-active ribozyme which

hybridizes to a Rev binding primate lentivirus **nucleic acid**, wherein said trans-active ribozyme comprises a Rev-binding **nucleic acid** which is less **cytotoxic** than a full-length Rev response element.

11. The molecule of claim 10, wherein said molecule is a targeted **HIV** chimeric **nucleic acid**, and wherein said trans-active ribozyme cleaves an **HIV nucleic acid** and provides greater viral inhibition as compared to a ribozyme which cleaves the same site of said **HIV nucleic acid** but which lacks a Rev-binding **nucleic acid** sequence.

12. The molecule of claim 10 wherein said molecule, when transfected into a cell culture and expressed in the cell culture, provides inhibition of a Rev-binding primate lentivirus in the cell culture for more than 15 weeks after the transfection.

13. The molecule of claim 10, wherein said molecule, when transfected into a cell culture and expressed in the cell culture, is not **cytotoxic** for at least 15 weeks following transfection.

14. The molecule of claim 10, wherein said trans-active ribozyme is a hairpin ribozyme.

15. The molecule of claim 10, wherein said molecule further comprises an anti-sense **nucleic acid** which specifically hybridizes to a **nucleic acid** encoded by the Rev-binding primate lentivirus.

16. A molecule comprising a trans-acting ribozyme and an SL II **nucleic acid**, which molecule inhibits replication of a Rev-binding primate lentivirus in eukaryotic cells in cell culture.

17. The molecule of claim 16, which molecule further comprises an anti-sense **nucleic acid** which specifically hybridizes to a **nucleic acid** encoded by the Rev-binding primate lentivirus.

18. The molecule of claim 16, wherein said molecule comprises a plurality of SL II nucleic acids.

19. A recombinant transcription cassette comprising the molecule of claim 10.

20. A vector comprising the molecule of claim 10, wherein said vector further comprises nucleic acids selected from the group consisting of the **HIV** packaging site and the AAV ITR.

21. A recombinant eukaryotic cell in culture which comprises a molecule which encodes a trans-active ribozyme which hybridizes to a **nucleic acid** of a Rev-binding primate lentivirus, wherein said trans-active ribozyme comprises a Rev-binding **nucleic acid** which is less **cytotoxic** than a full-length Rev response element.

22. The recombinant eukaryotic cell of claim 21, wherein said Rev-binding **nucleic acid** is an SL II **nucleic acid**.

23. The recombinant eukaryotic cell of claim 21, wherein said molecule, when expressed in a cell culture in vitro, provides viral inhibition to the cell culture for more than 15 weeks.

24. A recombinant eukaryotic cell in culture which stably expresses a molecule which molecule comprises an SL II **nucleic acid** and a trans-active ribozyme which hybridizes to a **nucleic acid** of a Rev-binding primate lentivirus.

25. The cell of claim 24 wherein said cell is a CD4+ cell selected from the group consisting of monocytes, lymphocytes and macrophages.

L27 ANSWER 23 OF 33 USPATFULL on STN

1999:109965 Induction of CTLs specific for natural antigens by cross priming immunization.

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US 5951975 19990914
APPLICATION: US 1996-675332 19960628 (8) <--
DOCUMENT TYPE: Utility; Granted.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to prophylactic and therapeutic methods of anti-tumor immunization. These methods are based on cross-priming a mammalian host to natural MHC class I restricted tumor antigens with an artificial tumor antigen. A primary tumor is resected from the patient and a population of tumor cells are cultured in vitro. These cultured tumor cells are loaded with an artificial target antigen. The loaded tumor cells are inactivated and introduced into the patient either simultaneous or subsequent to a direct immunization of the patient with the same or substantially the same artificial target antigen. This method of coupled host immunization promotes a tumor specific **cytotoxic** T lymphocyte (**CTL**) immune response against multiple, undefined natural tumor antigens expressed on the unmodified tumor cell surface.

CLM What is claimed is:

1. A method of eliciting an immune response in a mammalian host capable of generating an immune response which comprises: a) immunizing firstly said mammalian host with a foreign artificial target antigen in a form promoting a **CTL**-mediated response; b) culturing in vitro a population of tumor cells; c) engineering said cultured tumor cells to include said foreign artificial target antigen within said cultured tumor cells such that said engineered cultured tumor cells promote presentation of said foreign artificial target antigen on the cell surface; d) inactivating said population of engineered cultured tumor cells; e) immunizing secondly said mammalian host with the inactivated population of said engineered cultured tumor cells; wherein an immune response against unmodified tumor cells is elicited as a result of said immunizing steps.

2. The method of claim 1 where said mammalian host is a human.

3. The method of claim 2 wherein said foreign artificial target antigen of step (a) is presented to said mammalian host as a particulate complex.

4. The method of claim 3 wherein said foreign artificial target antigen of step (c) is introduced to said cultured tumor cells by peptide pulsing.

5. The method of claim 3 wherein said foreign artificial target antigen of step (c) is introduced to said cultured tumor cells by transfection of a **nucleic acid** molecule expressing effective amounts of said foreign artificial target antigen.

6. The method of claim 2 wherein said foreign artificial target antigen of step (c) is introduced to said cultured tumor cells by transfection of a **nucleic acid** molecule expressing effective amounts of said foreign artificial target antigen.

7. The method of claim 2 wherein said foreign artificial target antigen of step (c) is introduced to said cultured tumor cells by peptide pulsing.

8. The method of claim 1 wherein said foreign artificial target antigen is a tumor antigen selected from the group consisting of Melan-A, p53, CEA, gp100, MAGE-1 and MAGE-2.

9. The method of claim 1 wherein said foreign artificial target antigen is a viral antigen selected from the group consisting of **HIV** gp120, **HIV** gp100, Influenza virus nucleoprotein and Hepatitis B surface antigen.

10. The method of claim 1 wherein said foreign artificial target antigen is an **immunogenic** foreign antigen selected from the group consisting of chicken ovalbumin and keyhole limpit hemocyanin.

11. The method of claim 1 wherein said foreign artificial target antigen is chicken ovalbumin.

12. A method of eliciting an immune response in a mammalian host capable of generating an immune response which comprises: a) culturing in vitro a population of tumor cells; b) engineering said cultured tumor cells to include a foreign artificial target antigen within said cultured tumor cells such that said engineered cultured tumor cells promote presentation of said foreign artificial target antigens on the cell surface; c) inactivating said population of engineered cultured tumor cells; d) immunizing said mammalian host first with an inactivated population of said engineered cultured tumor cells and second with said foreign artificial target antigen in a form promoting a **CTL**-mediated response; wherein an immune response against unmodified tumor cells is elicited as a result of said immunizing steps.

13. The method of claim 12 where said mammalian host is a human.

14. The method of claim 13 wherein said foreign artificial target antigen of step (d) is presented to said mammalian host as a particulate complex.

15. The method of claim 14 wherein said foreign artificial target antigen of step (b) is introduced to said cultured tumor cells by transfection of a **nucleic acid** molecule expressing effective amounts of said foreign artificial target antigen.

16. The method of claim 14 wherein said foreign artificial target antigen of step (b) is introduced to said cultured tumor cells by peptide pulsing.

17. The method of claim 13 wherein said foreign artificial target antigen of step (b) is introduced to said cultured tumor cells by transfection of a **nucleic acid** molecule expressing effective amounts of said foreign artificial target antigen.

18. The method of claim 13 wherein said foreign artificial target antigen of step (b) is introduced to said cultured tumor cells by peptide pulsing.

19. The method of claim 12 wherein said foreign artificial target antigen is a tumor antigen selected from the group consisting of Melan-A, p53, CEA, gp100, MAGE-1 and MAGE-2.

20. The method of claim 12 wherein said foreign artificial target antigen is a viral antigen selected from the group consisting of **HIV** gp120, **HIV** gp100, Influenza virus nucleoprotein and Hepatitis B surface antigen.

21. The method of claim 12 wherein said foreign artificial target antigen is an **immunogenic** foreign antigen selected from the group consisting of chicken ovalbumin and keyhole limpit hemocyanin.

22. The method of claim 12 wherein said foreign artificial target antigen is chicken ovalbumin.

L27 ANSWER 26 OF 33 USPATFULL on STN
1999:85264 Vectors for gene delivery.

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US 5928913 19990727
APPLICATION: US 1996-621501 19960325 (8) <--
PRIORITY: GB 1995-5892 19950323
US 1995-29P 19950608 (60)
DOCUMENT TYPE: Utility; Granted.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Herpesvirus amplicon preparations comprise an origin of replication, a packaging sequence, and at least one inserted gene under control of a promoter, suitable for use as an **immunogen** or **vaccine**, in association with helper herpesvirus or DNA, wherein the associated helper virus is of restricted replication competence in a normal host cell; for example where the associated helper virus has an inactivating defect in respect of a gene essential for production of infectious new virus particles, and where the amplicon carries an inserted gene necessary for the propagation of the helper virus.

CLM What is claimed is:

1. A preparation of a herpesvirus amplicon comprising an origin of replication, a packaging sequence, and at least one inserted gene encoding an antigen or an immunomodulatory protein under control of a promoter, in association with helper herpesvirus of **DNA** thereof, wherein the associated helper virus has an inactivating defect in respect of a gene that is essential for the production of infectious new virus particles, such that the helper virus cannot cause production of infectious new virus particles except when said virus infects recombinant complementing host cells which have been made to carry and can express a gene that provides the function of said essential viral gene.

2. The preparation according to claim 1, wherein the essential viral gene is an essential viral glycoprotein, e.g. gH, gD, gB or gL or a homologue thereof.

3. The preparation according to claim 1, wherein said inserted gene encodes an immunomodulatory protein selected from cytokines, chemokines; and immune system accessory molecules and adhesion molecules and their receptors.

4. The amplicon preparation according to claim 1 wherein the amplicon encodes a gene for a function needed for helper virus replication, so that said preparation can be propagated in a host cell culture under conditions where the amplicon is essential to propagation of the helper virus.

5. The preparation according to claim 1, wherein the helper virus is in the form of **DNA** that has been cut with restriction endonuclease in a nonessential site, to restrict replication of the helper virus.

6. A method of in-vitro expansion of **cytotoxic** T cells, which comprises contacting T-cells to be used for said expansion with an amplicon preparation according to claim 1, whereby said **cytotoxic** T-cells are expanded.

7. The preparation according to claim 1, wherein said inserted gene encodes a heterologous antigen.

8. The preparation according to claim 7, wherein said heterologous antigen comprises a tumor-associated antigen.

9. The preparation according to claim 7, wherein said heterologous

antigen comprises a viral antigen.

10. The preparation according to claim 9, wherein said amplicon preparation comprises a mixture of amplicons encoding a plurality of viral antigens, e.g. multiple antigens from a virus heterlogous to the amplicon, e.g. Influenza virus or **HIV** or SIV or a hepatitis C virus.

11. A pharmaceutical preparation comprising a preparation according to claim 1.

12. The pharmaceutical preparation according to claim 11, for use as an **immunogen**, such as a **vaccine** or **vaccine** adjuvant.

13. A preparation of a herpesvirus amplicon comprising an origin of replication, a packaging sequence, and at least one inserted gene under control of a promoter, in association with a helper virus or **DNA** thereof, wherein the associated helper virus has an inactivating defect in respect of a gene that is essential for the production of infectious new virus particles, such that the helper virus cannot cause production of infectious new virus particles except when said helper virus infects recombinant complementing host cells which have been made to carry and can express a gene that provides the function of said essential viral gene; and wherein the amplicon carries an inserted gene necessary for the propagation of the helper virus.

14. The preparation according to claim 13, wherein the amplicon carries an inserted TK gene, the helper virus is TK- and is also a deletant in respect of an essential viral glycoprotein, whereby the amplicon is necessary for the propagation of the helper virus when the preparation is grown on TK-cells in the presence of methotrexate.

15. The preparation according to claim 13 wherein the genes of the helper virus and of said herpesvirus amplicon taken together are defective in respect of an essential viral gene function.

16. The preparation according to claim 15, wherein the amplicon carries an inserted first essential viral gene, the helper virus is a deletant in respect of the corresponding first essential viral gene and is also a deletant in respect of a second essential viral gene, whereby the amplicon is necessary for the propagation of the helper virus when the preparation is grown on cells complemented in respect of the function of the second essential viral gene.

17. The preparation according to claim 16, wherein the first essential viral gene encodes an essential viral glycoprotein and the second essential viral gene also encodes an essential viral glycoprotein (different from that encoded by the first essential viral gene); e.g. gD and gH respectively.

L27 ANSWER 27 OF 33 USPATFULL on STN
1999:69784 Desmin enhancer sequences, vectors comprising these sequences and their uses in compositions for the expression of nucleotide sequences in transfected cells.
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Institut Pasteur, Paris Cedex, France (non-U.S. corporation)Universite Paris 7, Paris Cedex, France (non-U.S. corporation)
US 5914395 19990622
WO 9626284 19960829
APPLICATION: US 1997-894228 19970912 (8) <--
WO 1996-FR261 19960216 19970912 PCT 371 date 19970912 PCT 102(e) date<--
PRIORITY: FR 1995-1937 19950220
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention teaches modified desmin enhancer sequences which yield

high level expression of operably linked DNA sequences. The claimed modified desmin enhancer sequences may be operably linked to genes encoding a protein. Further these modified desmin enhancer sequences may be placed into vectors including plasmids and transformed into cells including bacteria or myoblasts. Finally, these modified desmin enhancers may be used in methods of expression of proteins in the transformed bacteria or myoblasts.

CLM What is claimed is:

1. A single or double stranded enhancer **DNA** sequence comprising the following nucleotide sequence: 5'-TCTATAAATAX_1 X_2 X_3 GCY_1 Y_2 Y_3 GGTATTTGGGGTTGGCAGCTGTT-3' (SEQ ID NO: 1) wherein X_1 is G, X_2 is C or G, X_3 is C or A, Y_1 is T or C, Y_2 is C or G, and Y_3 is T or C.

2. A single or double stranded enhancer **DNA** sequence comprising the following nucleotide sequence: 5'-TCTATAAATAX_1 X_2 X_3 GCY_1 Y_2 Y_3 GGTATTTGGGGTTGGCAGCTGTT-3' (SEQ ID NO: 1) wherein X_1 is C or G, X_2 is G, X_3 is C or A, Y_1 is T or C, Y_2 is C or G, and Y_3 is T or C.

3. A single or double stranded enhancer **DNA** sequence comprising the following nucleotide sequence: 5'-TCTATAAATAX_1 X_2 X_3 GCY_1 Y_2 Y_3 GGTATTTGGGGTTGGCAGCTGTT-3' (SEQ ID NO: 1) wherein X_1 is C or G, X_2 is C or G, X_3 is A, Y_1 is T or C, Y_2 is C or G, and Y_3 is T or C.

4. A single or double stranded enhancer **DNA** sequence comprising the following nucleotide sequence: 5'-TCTATAAATAX_1 X_2 X_3 GCY_1 Y_2 Y_3 GGTATTTGGGGTTGGCAGCTGTT-3' (SEQ ID NO: 1) wherein X_1 is C or G, X_2 is C or G, X_3 is C or A, Y_1 is C, Y_2 is C or G, and Y_3 is T or C.

5. A single or double stranded enhancer **DNA** sequence comprising the following (SEQ ID NO: 1) nucleotide sequence: 5'-TCTATAAATAX_1 X_2 X_3 GCY_1 Y_2 Y_3 GGTATTTGGGGTTGGCAGCTGTT-3' wherein X_1 is C or G, X_2 is C or G, X_3 is C or A, Y_1 is T or C, Y_2 is G, and Y_3 is T or C.

6. A single or double stranded enhancer **DNA** sequence comprising the following nucleotide sequence: 5'-TCTATAAATAX_1 X_2 X_3 GCY_1 Y_2 Y_3 GGTATTTGGGGTTGGCAGCTGTT-3' (SEQ ID NO: 1) wherein X_1 is C or G, X_2 is C or G, X_3 is C or A, Y_1 is T or C, Y_2 is C or G, and Y_3 is C.

7. A **DNA** sequence comprising the enhancer of claim 1 operably linked to a gene encoding a protein.

8. A **DNA** sequence comprising the enhancer of claim 2 operably linked to a gene encoding a protein.

9. A **DNA** sequence comprising the enhancer of claim 3 operably linked to a gene encoding a protein.

10. A **DNA** sequence comprising the enhancer of claim 4 operably linked to a gene encoding a protein.

11. A **DNA** sequence comprising the enhancer of claim 5 operably linked to a gene encoding a protein.

12. A **DNA** sequence comprising the enhancer of claim 6 operably linked to a gene encoding a protein.

13. The **DNA** sequence of claim 7, wherein the gene encodes a bacterial antigen, a viral antigen, an **HIV**-1 protein, a portion of an **HIV**-1 protein, an interleukin, a fibroblast growth factor, a nerve growth factor, a protein which is capable of inducing an immune, humoral or **cytotoxic** response, or a protein which allow complementary gene activity in a gene normally expressed in an individual to be treated.

14. The **DNA** sequence of claim 8, wherein the gene encodes a bacterial antigen, a viral antigen, an **HIV**-1 protein, a portion of an **HIV**-1 protein, an interleukin, a fibroblast growth factor, a nerve growth factor, a protein which is capable of inducing an immune, humoral or **cytotoxic** response, or a protein which allow complementary gene activity in a gene normally expressed in an individual to be treated.

15. The **DNA** sequence of claim 9, wherein the gene encodes a bacterial antigen, a viral antigen, an **HIV**-1 protein, a portion of an **HIV**-1 protein, an interleukin, a fibroblast growth factor, a nerve growth factor, a protein which is capable of inducing an immune, humoral or **cytotoxic** response, or a protein which allow complementary gene activity in a gene normally expressed in an individual to be treated.

16. The **DNA** sequence of claim 10, wherein the gene encodes a bacterial antigen, a viral antigen, an **HIV**-1 protein, a portion of an **HIV**-1 protein, an interleukin, a fibroblast growth factor, a nerve growth factor, a protein which is capable of inducing an immune, humoral or **cytotoxic** response, or a protein which allow complementary gene activity in a gene normally expressed in an individual to be treated.

17. The **DNA** sequence of claim 11, wherein the gene encodes a bacterial antigen, a viral antigen, an **HIV**-1 protein, a portion of an **HIV**-1 protein, an interleukin, a fibroblast growth factor, a nerve growth factor, a protein which is capable of inducing an immune, humoral or **cytotoxic** response, or a protein which allow complementary gene activity in a gene normally expressed in an individual to be treated.

18. The **DNA** sequence of claim 12, wherein the gene encodes a bacterial antigen, a viral antigen, an **HIV**-1 protein, a portion of an **HIV**-1 protein, an interleukin, a fibroblast growth factor, a nerve growth factor, a protein which is capable of inducing an immune, humoral or **cytotoxic** response, or a protein which allow complementary gene activity in a gene normally expressed in an individual to be treated.

19. A vector comprising the **DNA** sequence of claim 7.

20. A vector comprising the **DNA** sequence of claim 8.

21. A vector comprising the **DNA** sequence of claim 9.

22. A vector comprising the **DNA** sequence of claim 10.

23. A vector comprising the **DNA** sequence of claim 11.

24. A vector comprising the **DNA** sequence of claim 12.

25. The vector of claim 19, which is a plasmid.

26. The vector of claim 20, which is a plasmid.

27. The vector of claim 21, which is a plasmid.

28. The vector of claim 22, which is a plasmid.

29. The vector of claim 23, which is a plasmid.

30. The vector of claim 24, which is a plasmid.

31. A microorganism transformed with the vector of claim 19.

32. A microorganism transformed with the vector of claim 20.

33. A microorganism transformed with the vector of claim 21.

34. A microorganism transformed with the vector of claim 22.

35. A microorganism transformed with the vector of claim 23.

36. A microorganism transformed with the vector of claim 24.

37. The microorganism of claim 31, which is Escherichia coli.

38. The microorganism of claim 32, which is Escherichia coli.

39. The microorganism of claim 33, which is Escherichia coli.

40. The microorganism of claim 34, which is Escherichia coli.

41. The microorganism of claim 35, which is Escherichia coli.

42. The microorganism of claim 36, which is Escherichia coli.

43. A muscle cell transformed with the vector of claim 19.

44. A muscle cell transformed with the vector of claim 20.

45. A muscle cell transformed with the vector of claim 21.

46. A muscle cell transformed with the vector of claim 22.

47. A muscle cell transformed with the vector of claim 23.

48. A muscle cell transformed with the vector of claim 24.

49. The muscle cell of claim 43, which is a myoblast or a myotube.

50. The muscle cell of claim 44, which is a myoblast or a myotube.

51. The muscle cell of claim 45, which is a myoblast or a myotube.

52. The muscle cell of claim 46, which is a myoblast or a myotube.

53. The muscle cell of claim 47, which is a myoblast or a myotube.

54. The muscle cell of claim 48, which is a myoblast or a myotube.

55. A method of expressing a protein, comprising culturing the transformed microorganism of claim 31, wherein said protein encoded by said gene is expressed.

56. A method of expressing a protein, comprising culturing the transformed microorganism of claim 32, wherein said protein encoded by said gene is expressed.

57. A method of expressing a protein, comprising culturing the transformed microorganism of claim 33, wherein said protein encoded by said gene is expressed.

58. A method of expressing a protein, comprising culturing the transformed microorganism of claim 34, wherein said protein encoded by said gene is expressed.

59. A method of expressing a protein, comprising culturing the transformed microorganism of claim 35, wherein said protein encoded by

said gene is expressed.

60. A method of expressing a protein, comprising culturing the transformed microorganism of claim 36, wherein said protein encoded by said gene is expressed.

61. A method of expressing a protein, comprising culturing the transformed muscle cell of claim 43, wherein said protein encoded by said gene is expressed.

62. A method of expressing a protein, comprising culturing the transformed muscle cell of claim 44, wherein said protein encoded by said gene is expressed.

63. A method of expressing a protein, comprising culturing the transformed muscle cell of claim 45, wherein said protein encoded by said gene is expressed.

64. A method of expressing a protein, comprising culturing the transformed muscle cell of claim 46, wherein said protein encoded by said gene is expressed.

65. A method of expressing a protein, comprising culturing the transformed muscle cell of claim 47, wherein said protein encoded by said gene is expressed.

66. A method of expressing a protein, comprising culturing the transformed muscle cell of claim 48, wherein said protein encoded by said gene is expressed.

67. A single or double stranded enhancer **DNA** sequence consisting of the following nucleotide sequence: 5'-TCTATAAATAX_1 X_2 X_3 GCY_1 Y_2 Y_3 GGTATTTGGGGTTGGCAGCTGTT-3' (SEQ ID NO: 1) wherein X_1 is C or G, X_2 is C or G, X_3 is C or A, Y_1 is T or C, Y_2 is C or G, and Y_3 is T or C.

L27 ANSWER 28 OF 33 USPATFULL on STN
1999:4042 Anti-acids secretory recombinant BCG **vaccine**.

Matsuo, Kazuhiro, Kawasaki, Japan
Chujo, Yoshitomo, Kawasaki, Japan
Yamazaki, Akihiro, Kawasaki, Japan
Honda, Mitsuo, Mitaka, Japan
Yamazaki, Shudo, Higashiyamato, Japan
Tasaka, Hiromichi, Kure, Japan
Ajinomoto Co., Inc., Tokyo, Japan (non-U.S. corporation)Japan as represented by Director General of Agency of National Institute of Health, Tokyo, Japan (non-U.S. corporation)

US 5858369 19990112
APPLICATION: US 1997-975699 19971121 (8) <--
PRIORITY: JP 1994-178462 19940729
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A **vaccine** containing Mycobacterium bovis BCG which secretes a fusion protein to be obtained by inserting a foreign antigen peptide into the molecular surface of a secretory protein, a carrier, having a signal peptide. BCG constituting the present invention secretes a fusion protein to be obtained by inserting a foreign antigen peptide into the molecular surface of an α-antigen derived from mycobacteria. Said fusion protein has significantly increased antigenicity and **immunogenicity**. Therefore, when it is inoculated into animals, it is efficiently recognized by B cells which recognize said antigen, thereby effectively inducing the production of an antibody to said antigen. When said BCG itself is inoculated into animals, it continuously secretes said fusion protein in the bodies of the animals while continuously

propagating therein. Therefore, said BCG is an extremely useful **vaccine**.

CLM What is claimed is:

1. An **immunogenic** composition comprising Mycobacterium bovis BCG which secretes a fusion protein, wherein the fusion protein is an α-antigen of mycobacteria into which a foreign antigenic peptide has been inserted between adjacent amino acids in a region between position 184 to 203 of the amino acid sequence of the α-antigen.

2. The **immunogenic** composition of claim 1, wherein the foreign antigenic peptide is inserted between residues 184 and 185 of the amino acid sequence of the α-antigen.

3. The **immunogenic** composition of claim 2, wherein residue 184 is Ser and residue 185 is Asp.

4. The **immunogenic** composition of claim 1, wherein the α-antigen is the α-antigen of Mycobacterium kansasii.

5. The **immunogenic** composition of claim 1, wherein the foreign antigenic peptide has a length of at most 19 amino acid residues.

6. The **immunogenic** composition of claim 1, wherein the foreign antigenic peptide is inserted into the molecular surface of the α-antigen.

7. The **immunogenic** composition of claim 1, wherein the foreign antigenic peptide is an antigenic peptide of an **HIV**-1 surface antigen.

8. The **immunogenic** composition of claim 7, wherein the foreign antigenic peptide comprises the third variable region of **HIV**-1.

9. The **immunogenic** composition of claim 8, wherein the foreign antigenic peptide has the amino acid sequence of SEQ ID NO: 1.

10. The **immunogenic** composition of claim 8, wherein the foreign antigenic peptide has the amino acid sequence of SEQ ID NO: 14, 15, 16, 17 or 18.

11. The **immunogenic** composition of claim 8, wherein the foreign antigenic peptide has the amino acid sequence of SEQ ID NO: 13.

12. A method of inducing an immune response, comprising administering an amount of the **immunogenic** composition of claim 1 to a patient effective for inducing an immune response.

13. A method of inducing an immune response, comprising administering an amount of the **immunogenic** composition of claim 7 to a patient effective for inducing an immune response.

14. A method of inducing antibody production, comprising administering an amount of the **immunogenic** composition of claim 1 to a patient effective for inducing antibody production.

15. A method of inducing **cytotoxic** T lymphocytes, comprising administering an amount of the **immunogenic** composition of claim 1 to a patient effective for inducing **cytotoxic** T lymphocytes.

16. A method of producing the **immunogenic** composition of claim 1, comprising transforming Mycobacterium bovis BCG with a **DNA** sequence encoding a fusion protein, wherein the fusion protein is an α-antigen of a mycobacteria into which a foreign antigenic peptide has been inserted between adjacent amino acids in a region between position 184 to 203 of the amino acid sequence of the α-antigen.

1998:138699 Method for production of high titer virus and high efficiency retroviral mediated transduction of mammalian cells.

Finer, Mitchell H., San Carlos, CA, United States
Roberts, Margo R., San Francisco, CA, United States
Dull, Thomas J., San Francisco, CA, United States
Zsebo, Krisztina M., Woodside, CA, United States
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Cell Genesys, Inc., Foster City, CA, United States (U.S. corporation)

US 5834256 19981110
APPLICATION: US 1993-76299 19930611 (8) <--
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention provides a novel retroviral packaging system, in which retroviral packaging constructs and packagable vector transcripts are produced from high expression plasmids by transfection in human cells. High titers of recombinant retrovirus are produced in infected cells. The methods of the invention include the use of the novel retroviral constructs to transduce primary human cells, including T cells and bone marrow stem cells, with foreign genes by cocultivation at high efficiencies. The invention is useful for the rapid production of high viral supernatants, and to transduce with high efficiency cells that are refractory to transduction by conventional means.

CLM What is claimed is:

1. A method for transducing, mammalian target cells with foreign genes, said method comprising: A) transient cotransfection of a first population of mammalian cells that can produce virus with: (i) at least one retroviral packaging plasmid comprising at least one retroviral helper **DNA** sequence derived from a replication-incompetent retroviral genome encoding in trans all virion proteins required for packaging a replication-incompetent retroviral vector at high titer without the production of replication competent helper virus said retroviral helper **DNA** sequence lacking the region encoding the native enhancer and/or promoter of the viral 5' LTR of said virus and lacking both the psi function sequence responsible for packaging helper genome and the 3' LTR, and encoding a foreign enhancer and/or promoter functional in a selected mammalian cell, and a SV40 polyadenylation site; and (ii) a retroviral vector encoding a foreign gene to produce replication-defective recombinant retroviral vectors carrying said foreign gene in said first population of mammalian cells; and B) cocultivation of said first population of mammalian cells producing replication-defective recombinant retroviral vectors carrying said foreign gene with a second population of mammalian target cells, to transduce said second population of target cells with said foreign gene, whereby target cells transduced with said foreign gene are obtained.

2. The method of claim 1, wherein said target cells are selected from the group consisting of lymphocytes, human hematopoietic stem cells, fibroblasts, epithelial cells, endothelial cells, myoblasts, retinal epithelial cells, islets of Langerhans, adrenal medulla cells, osteoblasts, osteoclasts, neurons, glial cells, ganglion cells, embryonic stem cells, and hepatocytes.

3. The method of claim 1, wherein said population of mammalian target cells are human cells.

4. The method of claim 1, wherein said population of mammalian target cells are human hematopoietic stem cells.

5. The method of claim 1, wherein said first population of mammalian cells are human embryonic kidney cells.

6. The method of claim 1, wherein said retroviral genome is a leukemia viral genome selected from the group consisting of Moloney murine leukemia virus (MMLV), **Human immunodeficiency virus** (**HIV**) and

Gibbon ape leukemia virus (GALV).

7. The method of claim 1, wherein said retroviral packaging plasmid comprises two retroviral helper **DNA** sequences.

8. The method of claim 1, wherein said foreign gene is selected from the group consisting of gene coding growth factors, lymphokines, hormones and coagulation factors.

9. The method of claim 1, wherein said foreign gene encodes a chimeric T cell receptor.

10. The method of claim 3 wherein said human target cells are lymphocytes.

11. The method of claim 10, wherein said lymphocytes are T cells.

12. The method of claim 10, wherein said lymphocytes are selected from the group consisting of CD8 positive **cytotoxic** T cells, CD4 positive T cells and tumor-infiltrating lymphocytes.

13. The method of claim 11, wherein said T cells are **cytotoxic** T cells.

14. The method of claim 5, wherein said human embryonic kidney cells are 293 cells.

15. The method of claim 14 wherein said 293 cells are tsa201 cells.

16. The method of claim 6, wherein said foreign enhancer is the human cytomegalovirus (CMV) immediate early enhancer and said promoter is the native MMLV promoter.

17. The method of claim 6, wherein said foreign enhancer and promoter is the human CMV immediate early enhancer and promoter.

18. The method of claim 6, wherein said foreign enhancer and promoter is the Moloney murine sarcoma virus (MMSV) enhancer and promoter.

19. The method of claim 7, wherein a first helper sequence codes for ecotropic MMLV gag and pol proteins and a second helper sequence codes for env proteins, or combinations thereof, selected from virus of the group consisting of xenotropic murine leukemia virus, amphotropic murine leukemia virus, ecotropic murine leukemia virus, polytropic murine leukemia virus, 10A1 murine leukemia virus, GALV, **HIV**, Vesicular Stomatitis Virus (VSV), human T cell leukemia virus (HTLV) type I and HTLV type II.

20. The method of claim 7 wherein a first helper sequence codes for **HIV** gag and pol proteins or GALV gag and pol proteins and a second helper sequence codes for env proteins, or combinations thereof, selected from virus of the group consisting of xenotropic murine leukemia virus, amphotropic murine leukemia virus, ecotropic murine leukemia virus, polytropic murine leukemia virus, 10A1 murine leukemia virus, GALV, **HIV**, Vesicular Stomatitis Virus, human T cell leukemia virus (HTLV) type I and HTLV type II.

21. The method of claim 9, wherein said chimeric T cell receptor is a receptor encoded by a **DNA** sequence comprising in reading frame: a sequence encoding a signal sequence; a sequence encoding a non-MHC restricted extracellular surface membrane protein domain binding specifically to at least one ligand; a sequence encoding a transmembrane domain; and a sequence encoding a cytoplasmic signal-transducing domain of a protein that activates an intracellular messenger system.

22. The method of claim 21, wherein said cytoplasmic domain is selected from the group consisting of gene coding the CD3 zeta chain, the eta

chain, the CD3 gamma chain, the CD3 delta chain and the CD3 epsilon chain.

23. The method of claim 21, wherein said cytoplasmic domain is the gamma chain of the FcεR1 receptor.

24. The method of claim 21, wherein said extracellular domain is a single-chain antibody, or functional portion thereof.

25. The method of claim 21, wherein said extracellular domain is a single-chain antibody specific for the **HIV** env glycoprotein and said cytoplasmic domain is zeta.

26. The method of claim 21, wherein said chimeric T cell receptor is a CD4/zeta receptor.

27. The method of claim 23, wherein said extracellular domain is a CD antigen.

28. The method of claim 27, wherein said extracellular domain is CD4 or CD8.

29. The method of claim 24, wherein said single-chain antibody is specific for the **HIV** env glycoprotein.

30. A method for transducing mammalian target cells with foreign genes, said method comprising: A) transient cotransfection of 293 cells with (i) at least one retroviral packaging plasmid comprising at least one retroviral helper **DNA** sequence derived from a replication-incompetent retroviral genome encoding in trans all virion proteins required for packaging a replication-incompetent retroviral vector at high titer, without the production of replication-competent helper virus, said retroviral helper **DNA** sequence lacking the region encoding the native enhancer and promoter of the viral 5' LTR of said virus and lacking both the psi function sequence responsible for packaging helper genome and the 3' LTR, and encoding a foreign enhancer and promoter functional in a selected mammalian cell and a SV40 polyadenylation site; and (ii) a retroviral vector encoding a foreign gene to produce replication-defective recombinant retroviral vectors carrying said foreign gene in said 293 cells; and B) cocultivation of said 293 cells producing replication-defective recombinant retroviral vectors carrying said foreign gene with a second population of mammalian target cells, to transduce said population of target cells with said foreign gene, whereby target cells efficiently transduced with said foreign gene are obtained.

31. The method of claim 30, wherein said target cells are human target cells.

32. The method of claim 31, wherein said human target cells are lymphocytes.

33. The method of claim 31, wherein said human target cells are hematopoietic stem cells.

34. A method for transducing mammalian target cells with foreign genes, said method comprising cocultivation of transfected 293 cells producing replication-defective recombinant retroviral vectors carrying a selected foreign gene with mammalian target cells, to transduce said target cells with said foreign gene, whereby target cells transduced with said foreign gene are obtained.

35. The method of claim 34, wherein said 293 cells are transiently cotransfected.

36. The method of claim 34, wherein said 293 cells are stably

transfected.

37. The method of claim 34, wherein said mammalian target cells are human cells.

38. The method of claim 34, wherein said 293 cells are transiently cotransfected with: (a) at least one retroviral packaging plasmid comprising at least one retroviral helper **DNA** sequence derived from a replication-incompetent retroviral genome encoding in trans all virion proteins required for packaging a replication-incompetent retroviral vector at high titer, without the production of replication-competent helper virus, said retroviral helper **DNA** sequence lacking the region encoding the native enhancer and promoter of the viral 5' LTR of said virus and lacking both the psi function sequence responsible for packaging helper genome and the 3' LTR, and encoding a foreign enhancer and promoter functional in a selected mammalian cell and a SV40 polyadenylation site; and (b) a retroviral vector encoding a foreign gene to produce replication-defective recombinant retroviral vectors carrying said foreign gene in said 293 cells.

39. The method of claim 37, wherein said human cells are lymphocytes.

40. The method of claim 37, wherein said human cells are hematopoietic stem cells.

41. A retroviral packaging plasmid for the production of high titers of recombinant retrovirus in human cells comprising at least one retroviral helper **DNA** sequence derived from a replication-incompetent retroviral genome encoding in trans all virion proteins required for packaging a replication-incompetent retroviral vector at high titer, without the production of replication-competent helper virus, said retroviral helper **DNA** sequence lacking the region encoding the native enhancer and promoter of the viral 5' LTR of said virus and lacking both the psi function sequence responsible for packaging helper genome and the 3' LTR, and encoding a foreign enhancer and promoter functional in a selected mammalian cell and a SV40 polyadenylation site.

42. The retroviral packaging plasmid of claim 41, wherein said retrovirus is a leukemia retrovirus.

43. The retroviral packaging plasmid according to claim 41 wherein said helper **DNA** sequence codes for ecotropic MMLV gag and pol, and an envelope protein, or combination thereof, selected from virus of the group consisting of xenotropic murine leukemia virus, amphotropic murine leukemia virus, ecotropic murine leukemia virus, polytropic murine leukemia virus, 10A1 murine leukemia virus, GALV, **HIV**, vesicular stomatitis virus, human T cell leukemia virus (HTLV) type I and HTLV type II.

44. A method for transiently producing replication-defective recombinant retrovirus in mammalian cells at high titer comprising introducing into mammalian cells that can produce virus at least one retroviral packaging plasmid according to claim 41 and a retroviral vector encoding a foreign gene, whereby mammalian cells containing said retroviral packaging plasmid and retroviral vector produce high titers of retrovirus for infection.

45. The retroviral packaging plasmid of claim 42, wherein said leukemia retrovirus is selected from the group consisting of Moloney murine leukemia viruses (MMLV), Gibbon ape leukemia viruses (GALV), and **HIV** viruses.

46. The retroviral packaging plasmid of claim 45, wherein said foreign enhancer is the human CMV immediate early enhancer and said promoter is the native MMLV promoter.

47. The retroviral packaging plasmid of claim 45, wherein said foreign enhancer and promoter is the human CMV immediate early enhancer and promoter.

48. The retroviral packaging plasmid of claim 45, wherein said foreign enhancer and promoter is the MMSV enhancer and promoter.

49. The retroviral packaging plasmid of claim 45, wherein said plasmid comprises two retroviral helper **DNA** sequences.

50. The retroviral packaging plasmid of claim 49, wherein a first helper sequence codes for ecotropic MMLV gag and pol proteins and a second helper sequence codes for env proteins, or combinations thereof, selected from virus of the group consisting of xenotropic murine leukemia virus, amphotropic murine leukemia virus, ecotropic murine leukemia virus, polytropic murine leukemia virus, 10A1 murine leukemia virus, GALV, **HIV**, Vesicular Stomatitis Virus (VSV), human T cell leukemia virus (HTLV) type I and HTLV type II.

51. The method of claim 44 wherein said mammalian cells are human cells.

52. A transfected cell producing replication-defective recombinant retroviruses at high titer, said cell prepared by the method of claim 44.

53. The method of claim 51, wherein said human cells are human embryonic kidney cells.

54. The method of claim 53, wherein said human embryonic kidney cells are 293 cells.

55. The method of claim 54 wherein said 293 cells are tsa201 cells.

56. The transfected cell of claim 52, wherein said cell is a human cell.

57. The transfected cell of claim 56, wherein said human cell is a human embryonic kidney cell.

58. The transfected cell of claim 57, wherein said embryonic kidney cell is a 293 cell.

59. The transfected cells of claim 58 wherein said 293 cells are tsa201 cells.

60. A replication-defective retroviral vector comprising in the 5' to 3' direction, a modified 5' MMLV LTR region wherein the U3 region of the 5' LTR is replaced with the U3 region of MMSV, viral gag sequences up to the Nar I site of MMLV, a retroviral splice acceptor and a 3' MMLV LTR region.

61. A replication-defective retroviral vector comprising in the 5' to 3' direction, a modified 5' MMLV LTR region wherein the 5' LTR is replaced with the human CMV immediate early enhancer/promoter fused to the MMLV R region by an oligonucleotide encoding nucleotides 19 (Sac I) to +1 of the human CMV promoter linked to nucleotides +1 to +32 (KpnI) of MMLV, viral gag sequences up to the Nar I site of MMLV, a retroviral splice acceptor and a MMLV 3' LTR region.

62. A replication-defective retroviral vector comprising a modification of the vector of claim 61 wherein the Sac I to Bst EII fragment of the vector of claim 64 is replaced with the Sac I to Bst EII fragment of vector LXSN.

63. A replication-defective retroviral vector comprising a modification of pIK1.1 which contains the SV40 T antigen polyadenylation site and the SV40 origin of replication, wherein said modification consists of an

insertion of the **DNA** sequence between the 5' LTR and 3' LTR of the vector of claim 61 between the SacI and EcoRI sites of pIK1.1.

64. A replication-defective retroviral vector comprising a modification of the pIK1.1 vector containing the SV40 T antigen polyadenylation site and the SV40 origin of replication, wherein the **DNA**, defined at its 5' end by the Sac I site in the human CMV promoter and defined at its 3' end by an Eco RI site located approximately 750 bp downstream of the 3' LTR of the vector of claim 62 is inserted, between the SacI and Eco RI sites of pIK1.1.

65. The retroviral vector of claim 64, wherein the splice acceptor is replaced with a transcriptional control element internal to the vector selected from the group consisting of a promoter, enhancer, enhancer/promoter and a dominant control region.

66. The retroviral vector of claim 60, 61, 62, 63 or 64 further comprising **DNA** encoding a foreign gene inserted downstream of said splice acceptor.

67. A replication-defective retroviral vector comprising a modification of pIK1.1 in which the sequences of pIK1.1 downstream of the human CMV immediate early enhancer/promoter and upstream of the SV40 origin of replication and SV40 polyadenylation site are replaced with a fragment of a first retroviral vector consisting of the 5' R region of the first retroviral vector up to a restriction site downstream of the 3' LTR of said first retroviral vector.

68. The replication-defective retroviral vector of claim 67, wherein said first retroviral vector is an MMLV vector.

69. The retroviral vector of claim 66 wherein said foreign gene encodes a chimeric T cell receptor.

70. The retroviral vector of claim 69 wherein said receptor is a CD4/zeta or single-chain antibody chain/zeta T cell receptor.

71. A method of using the replication-defective retroviral vector of claim 66 to express high levels of packagable genomic retroviral transcipts in mammalian cells comprising transiently cotransfecting a first population of mammalian cells with a packaging plasmid and said retroviral vector whereby said transcripts are produced.

72. A mammalian cell which produces recombinant retrovirus by the method of claim 71.

73. The method of claim 71, further comprising cocultivating said first population of mammalian cells with a second population of target cells to transduce said target cells with the foreign gene.

74. The mammalian cell according to claim 72, wherein said mammalian cell is a human cell.

75. The mammalian cell according to claim 74, wherein said human cell is a 293 cell.

76. The method of claim 73 wherein said target cells are lymphocytes.

77. A method for transducing mammalian target cells with foreign genes, said method comprising: A) transient cotransfection of a first population of mammalian cells that can produce virus with: (i) at least one retroviral packaging plasmid comprising at least one retroviral helper **DNA** sequence derived from a replication-incompetent retroviral genome encoding in trans all virion proteins required for packaging a replication-incompetent retroviral vector at high titer, without the production of replication-competent helper virus, said retroviral helper

DNA sequence lacking the region encoding the native enhancer and/or promoter of the viral 5' LTR of said virus and lacking both the psi function sequence responsible for packaging helper genome and the 3' LTR, and encoding a foreign enhancer and/or promoter functional in a selected mammalian cell, and a SV40 polyadenylation site; and (ii) a retroviral vector encoding a foreign gene to produce replication-defective recombinant retroviral vectors carrying said foreign gene in said first population of mammalian cells; B) separation of said first population of mammalian cells from cell supernatant; and C) incubating of said supernatant containing replication-defective recombinant retroviral vectors carrying said foreign gene with a second population of mammalian target cells, to transduce said second population of target cells with said foreign gene, whereby target cells transduced with said foreign gene are obtained.

78. The method of claim 77 wherein said first population of mammalian cells are human embryonic kidney cells.

79. The method of claim 77 wherein said retroviral packaging plasmid comprises two retroviral helper **DNA** sequences.

80. The method of claim 78 wherein said human embryonic kidney cells are 293 cells.

81. The method of claim 79 wherein a first helper sequence codes for ecotropic MMLV gag and pol proteins and a second helper sequence codes for env proteins, or combinations thereof, selected from virus of the group consisting of xenotropic murine leukemia virus, amphotropic murine leukemia virus, ecotropic murine leukemia virus, polytropic murine leukemia virus, 10A1 murine leukemia virus, GALV, **HIV**, Vesicular Stomatitis Virus, human T cell leukemia virus (HTLV) type I and HTLV type II.

82. The method of claim 79 wherein a first helper sequence codes for **HIV** gag and pol proteins or GALV gag and pol proteins and a second helper sequence codes for env proteins, or combinations thereof, selected from virus of the group consisting of xenotropic murine leukemia virus, amphotropic murine leukemia virus, ecotropic murine leukemia virus, polytropic murine leukemia virus, 10A1 murine leukemia virus, GALV, **HIV**, Vesicular Stomatitis Virus, human T cell leukemia virus (HTLV) type I and HTLV type II.

83. The retroviral vector of claim 65, further comprising **DNA** encoding a foreign gene inserted downstream of said transcriptional control element.

84. The retroviral vector of claim 83, wherein said foreign gene is a chimeric T cell receptor.

85. A method of using the retroviral vector of claim 83 to express high levels of packagable genomic retroviral transcripts in mammalian cells which produce virus comprising transiently cotransfecting a first population of mammalian cells with a packaging plasmid and said retroviral vector whereby said transcripts are produced.

86. The retroviral vector of claim 84, wherein said receptor is a CD4/zeta or single-chain antibody/zeta T cell receptor.

87. The method of claim 85, further comprising cocultivating said first population of mammalian cells with a second population of target cells to transduce said target cells with the foreign gene.

88. A mammalian cell producing recombinant retroviruses produced by the method of claim 85.

89. The method of claim 87, wherein said target cells are lymphocytes.

90. Retroviral packaging plasmid pIK6.1MMSVampac, having the structure shown in FIG. 1.

91. Retroviral packaging plasmid pIK6.1MCVampac, having the structure shown in FIG. 1.

92. Retroviral packaging plasmid pIK6.1gagpolATG, having the structure shown in FIG. 1.

93. Retroviral packaging plasmid pIK6.1amenvATG, having the structure shown in FIG. 1.

94. The method of claim 1, wherein said retroviral packaging plasmid is the retroviral packaging plasmid of claim 90, 91, 92 or 93.

95. A retroviral vector designated pRTD4.2.

96. A retroviral vector designated pRTD2.2.

97. A retroviral vector designated pRTD2.2SVG.

98. A retroviral vector designated pIKT2.2.

99. A retroviral vector designated pIKT2.2SVG.

L27 ANSWER 30 OF 33 USPATFULL on STN
1998:58087 Peptides capable of inducing immune response to **HIV**.
Takiguchi, Masafumi, Tokyo, Japan
Miwa, Kiyoshi, Kawasaki, Japan
Ajinomoto Co., Inc., Tokyo, Japan (non-U.S. corporation)
US 5756666 19980526
WO 9511255 19950427
APPLICATION: US 1996-615181 19960404 (8) <--
WO 1994-JP1756 19941019 19960404 PCT 371 date 19960404 PCT 102(e) date
PRIORITY: JP 1993-261302 19931019
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Herein disclosed is a peptide which is a fragment of the whole protein of **HIV**, the fragment being a peptide having a sequence of successive 8 to 11 amino acid residues, which corresponds to an HLA-binding motif, which actually binds to HLA and which can induce killer cells capable of attacking **HIV**-infected cells as target cells. The peptide is effective as an anti-AIDS agent for **preventing** and curing AIDS.

CLM What is claimed is:
1. A peptide fragment of an **HIV** protein which has a length of 8 to 11 amino acid residues, binds to HLA, and induces production of **cytotoxic** T lymphocytes against cells infected with **HIV**, wherein the second amino acid residue is Pro, and the C-terminal amino acid residue is selected from the group consisting of Tyr, Leu, Ile, Met, Phe and Ala.

2. The peptide fragment of claim 18, wherein the **HIV** protein is selected from the group consisting of pol, gag, vpr, vif, rev and env.

3. The peptide fragment of claim 1 having the sequence of SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 or 24.

4. A peptide fragment of an **HIV** protein which has a length of 8 to 11 amino acid residues, binds to HLA, and induces production of **cytotoxic** T lymphocytes against cells infected with **HIV**, wherein the second amino acid residue is selected from the group consisting of Pro, Ala and Gly, and the C-terminal amino acid residue is selected from the group consisting of Ile, Leu, Val, Phe and Met.

5. The peptide fragment of claim 4, wherein the **HIV** protein is selected from the group consisting of pol, gag, vpr, vif, rev and env.

6. The peptide fragment of claim 3 having the sequence of SEQ ID NO: 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45 or 46.

7. A peptide fragment of an **HIV** protein which has a length of 8 to 11 amino acid residues, binds to HLA, and induces production of **cytotoxic** T lymphocytes against cells infected with **HIV**, wherein the second amino acid residue is selected from the group consisting of Leu, Val, Tyr, and Phe, and the C-terminal amino acid residue is Arg.

8. The peptide fragment of claim 7, wherein the **HIV** protein is selected from the group consisting of pol, gag, vpr, vif, rev and env.

9. The peptide fragment of claim 5 having the sequence of SEQ ID NO: 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62 or 63.

10. An **immunogenic** composition, comprising the peptide fragment of claim 1 and a pharmaceutically acceptable carrier and/or a pharmaceutically acceptable diluent.

11. An **immunogenic** composition, comprising the peptide fragment of claim 4 and a pharmaceutically acceptable carrier and/or a pharmaceutically acceptable diluent.

12. An **immunogenic** composition, comprising the peptide fragment of claim 7 and a pharmaceutically acceptable carrier and/or a pharmaceutically acceptable diluent.

13. A method of inducing **cytotoxic** T lymphocytes comprising contacting the peptide fragment of claim 1 with peripheral blood lymphocytes having HLA-B antigens.

14. A method of inducing **cytotoxic** T lymphocytes comprising contacting the peptide fragment of claim 4 with peripheral blood lymphocytes having HLA-B antigens.

15. A method of inducing **cytotoxic** T lymphocytes comprising contacting the peptide fragment of claim 7 with peripheral blood lymphocytes having HLA-A antigens.

16. A method of inducing **cytotoxic** T lymphocytes, comprising administering the peptide fragment of claim 1 to a patient in need thereof.

17. A method of inducing **cytotoxic** T lymphocytes, comprising administering the peptide fragment of claim 4 to a patient in need thereof.

18. A method of inducing **cytotoxic** T lymphocytes, comprising administering the peptide fragment of claim 7 to a patient in need thereof.

19. A **DNA** encoding the peptide fragment of claim 1.

20. A **DNA** encoding the peptide fragment of claim 4.

21. A **DNA** encoding the peptide fragment of claim 7.

22. A method of screening peptides for induction of **cytotoxic** T lymphocytes comprising: contacting peptide fragments of an **HIV** protein having a length of 8 to 11 amino acid residues with cells that are deficient in transporter associated protein antigen and express HLA class I antigen; selecting peptides which maintain the expression of the

HLA class I antigen on the cells, and contacting the selected peptides with peripheral blood lymphocytes of a patient infected with **HIV**.

L27 ANSWER 31 OF 33 USPATFULL on STN
1998:17356 Method of potentiating cell-mediated immunity utilizing polyamine derivatives.

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US 5719193 19980217
APPLICATION: US 1995-422751 19950414 (8) <--
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention relates to a method of potentiating cell-mediated immunity which comprises administering to a patient a cell-mediated immunity potentiating amount of a compound of the formula:

$RHN{-}{-}Z{-}{-}NH{-}{-}(CH_2)_m{-}{-}NH{-}{-}Z{-}{-}NHR$

or a pharmaceutically acceptable salt thereof, wherein m is an integer 3 to 12, Z is a saturated C_2 -C_6 alkylene moiety of straight or branched chain configuration, each R group is independently H, a C_1 -C_6 saturated or unsaturated hydrocarbyl, or --$(CH_2)_x$ --(Ar)--X wherein X is H, C_1 -C_6 alkoxy, halogen, C_1 -C_4 alkyl, or --$S(O)_x$ R_1, x is an integer 0, 1 or 2, and R_1 is C_1 -C_6 alkyl.

CLM What is claimed is:

1. A method of potentiating cell-mediated immunity which comprises administering to a patient suffering from a viral disease an effective cell-mediated immunity potentiating amount of a compound of the formula: $RHN{-}{-}Z{-}{-}NH{-}{-}(CH_2)_m{-}{-}NH{-}{-}Z{-}{-}NHR$ or a pharmaceutically acceptable salt thereof, wherein m is an integer 3 to 12, Z is a saturated C_2 -C_6 alkylene moiety of straight or branched chain configuration, each R group is independently H, a C_1 -C_6 saturated or unsaturated hydrocarbyl, or --$(CH_2)_x$ --(Ar)--X wherein Ar is phenyl or naphthyl, X is H, C_1 -C_6 alkoxy, halogen, C_1 -C_4 alkyl, or --$S(O)_x$ R_1, wherein x is an integer 0, 1, or 2, and R_1 is C_1 -C_6 alkyl with the proviso that at least one of R must be other than H.

2. A method of potentiating the activity of effector cells of the cellular immune system which comprises administering to a patient suffering from a viral disease an effective effector cell potentiating amount of a compound of the formula: $RHN{-}{-}Z{-}{-}NH{-}{-}(CH_2)_m$ --NH--Z--NHR or a pharmaceutically acceptable salt thereof, wherein m is an integer 3 to 12, Z is a saturated C_2 -C_6 alkylene moiety of straight or branched chain configuration, each R group is independently H, a C_1 -C_6 saturated or unsaturated hydrocarbyl, or --$(CH_2)_x$ --(Ar)--X wherein X is H, C_1 -C_6 alkoxy, halogen, C_1 -C_4 alkyl or --$S(O)_x$ R_1, x is an integer 0, 1, or 2, and R_1 is C_1 -C_6 alkyl.

3. A method according to claim 2 wherein the effector cell potentiated is a T-cell.

4. A method according to claim 2 wherein the effector cell potentiated is a natural cell-mediated **cytotoxic** cell.

5. A method according to claim 2 wherein the effector cell potentiated is a macrophage.

6. The method according to claim 1, wherein Z is C_3.

7. The method according to claim 6, wherein m is 8.

8. The method according to claim 1, wherein R_1 is H, methyl or ethyl.

9. The method according to claim 1, wherein Z is an alkyl-substituted propylene chain.

10. The method according to claim 1, wherein Q is a saturated alkyl moiety comprising 1 to 3 carbon atoms of straight or branched chain configuration.

11. The method according to claim 1, wherein Z is C_2.

12. The method according to claim 1, wherein the compound is 1,18-Bis[(phenyl)methyl]-1,5,14,18-tetraazaoctadecane, or a pharmaceutically acceptable salt thereof.

13. The method according to claim 1, wherein the compound is 1,20-Bis[(phenyl)methyl]-1,6,15,20-tetraazaeicosane or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt thereof.

14. The method according to claim 1, wherein the compound is N,N'-Bis(3-aminobutyl)-1,8-octanediamine, or a pharmaceutically acceptable salt thereof.

15. The method according to claim 1, wherein the compound is N,N'-Bis[(3-ethyolamino)butyl]-1,7-diaminoheptane, or a pharmaceutically acceptable salt thereof.

16. The method according to claim 1, wherein the compound is 1,4,13,16-tetra(t-buyoxycarbonyl)-1,4,13,16-tetraazahexadecane, or a pharmaceutically acceptable salt thereof.

17. The method according to claim 1, wherein the compound as 1,18-Bis[(2-phenyl)ethyl]-1,5,14,18-tetraazaoctadecane, or a pharmaceutically acceptable salt thereof.

18. The method according to claim 1, wherein the compound as 1,18-Bis(phenyl)-1,5,14,18-tetraazaoctadecane, or a pharmaceutically acceptable salt thereof.

19. The method according to claim 1, wherein the compound is 1,18-Bis(2,3-butadienyl)-1,5,14,18-tetraazaoctadecane, or a pharmaceutically acceptable salt thereof.

20. The method according to claim 1, wherein the compound as 3,7,15,19-tetraazaeicosane, or a pharmaceutically acceptable salt thereof.

21. The method according to claim 1, wherein the compound is 3,17-dimethyl-2,6,14,18-tetraazanonadecane, or a pharmaceutically acceptable salt thereof.

22. The method according to claim 1, wherein the compound is 4,6-dimethyl-2,6,14,18-tetraazanonadecane, or a pharmaceutically acceptable salt thereof.

23. The method according to claim 1, wherein the viral disease is caused by an RNA virus or **DNA** virus.

24. The method according to claim 23, wherein the virus is influenza

type A, B or C, mumps, measles, rhinovirus, dengue, rubella, rabies, hepatitis virus A, or encephalitis virus.

25. The method according to claim 23, wherein the virus is **human immunodeficiency virus**.

26. The method according to claim 23, wherein the virus is HTLV-I, HTLV-II or HTLV-III.

27. The method according to claim 23, wherein the virus is herpes, **vaccinia**, pappiloma virus or hepatitis virus B.

28. The method according to claim 2, wherein the vital disease is caused by an RNA virus or **DNA** virus.

29. The method according to claim 28, wherein the virus is influenza type A, B or C, mumps, measles, rhinovirus, dengue, rubella, rabies, hepatitis virus A, or encephalitis virus.

30. The method according to claim 28, wherein the virus is **human immunodeficiency virus**.

31. The method according to claim 28, wherein the virus is HTLV-I, HTLV-II or HTLV-III.

32. The method according to claim 28, wherein the virus is herpes, **vaccinia**, pappiloma virus or hepatitis virus B.

L27 ANSWER 32 OF 33 USPATFULL on STN
96:116263 Autonomous parvovirus gene delivery vehicles and expression vectors.
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University of Colorado Foundation, Inc., Boulder, CO, United States (U.S. corporation)
US 5585254 19961217
APPLICATION: US 1993-42419 19930402 (8) <--
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to novel recombinant autonomous parvovirus vectors, novel recombinant virus particles, and novel gene delivery vehicles that can be used to selectively target heterologous nucleic acid sequences to desired cell types and to selectively express such sequences in such desired cell types. Recombinant autonomous parvovirus gene delivery vehicles are particularly advantageous for transient gene therapy, and are especially well-suited to treat diseases in which there is rapid cell growth, such as cancer. Also included is the use of recombinant vectors of the present invention to produce RNA and protein products in cell culture.

CLM What is claimed is:
1. A recombinant vector comprising **nucleic acid** sequences of an autonomous parvovirus joined to at least one heterologous **nucleic acid** sequence, said autonomous parvovirus **nucleic acid** sequences comprising functional left and right end inverted terminal repeats, said heterolegous **nucleic acid** sequence being located between and operably linked to said **nucleic acid** sequences comprising said left and right inverted terminal repeats, wherein said vector is in a non-integrating form when transferred into a cell.

2. The vector of claim 1, wherein said heterologous **nucleic acid** sequence is selected from the group consisting of a heterologous control element and a heterologous coding region, said heterologous control element being operably linked to said heterologous coding region.

3. The vector of claim 1, wherein said heterologous control element comprises a heterologous response element.

4. The vector of claim 1, wherein said heterologous **nucleic acid** sequence comprises a heterologous control element operatively linked to a heterologous coding region.

5. The vector of claim 1, wherein said heterologous **nucleic acid** sequence comprises at least one heterologous response element operatively linked to a promoter selected from the group consisting of an autonomous parvovirus promoter and a heterologous promoter.

6. The vector of claim 2, wherein said heterologous control element is operatively linked to at least one coding region selected from the group consisting of an autonomous parvovirus coding region and said heterologous coding region.

7. The vector of claim 2, wherein said heterologous coding region is operatively linked to a transcription control sequence selected from the group consisting of an autonomous parvovirus transcription control sequence that regulates the expression of parvovirus nonstructural polypeptide genes, an autonomous parvovirus transcription control sequence that regulates the expression of parvovirus structural polypeptide genes, and a heterologous transcription control sequence comprising a promoter and at least one heterologous response element.

8. The vector of claim 1, wherein said vector is packaged into a virus particle.

9. The vector of claim 1, wherein said parvovirus **nucleic acid** sequences are selected from the group consisting of LuIII parvovirus, minute virus of mice, hamster parvovirus, feline panleukopenia virus, canine parvovirus, porcine parvovirus, latent rat virus, mink enteritis virus, human parvovirus, bovine parvovirus, and Aleutian mink disease parvovirus **nucleic acid** sequences.

10. The vector of claim 1, wherein said parvovirus **nucleic acid** sequences are selected from the group consisting of LuIII parvovirus, minute virus of mice MVMi, minute virus of mice MVMp, and hamster parvovirus Hi **nucleic acid** sequences.

11. The vector of claim 1, wherein said parvovirus **nucleic acid** sequences comprise a LuIII parvovirus **nucleic acid** sequence.

12. The vector of claim 2, wherein said heterologous coding region is operatively linked to an autonomous parvovirus P4 transcription control sequence.

13. The vector of claim 2, wherein said heterologous coding region is operatively linked to a LuIII P4 transcription control sequence.

14. The vector of claim 1, wherein said heterologous **nucleic acid** sequence is selected from the group consisting of a cell-selective response element, a hormone receptor response element, an antibiotic response element, and a carbohydrate response element.

15. The vector of claim 14, wherein said cell-selective response element is capable of being activated by a trans-activating regulatory element selectively produced in a cell type to which said vector is targeted.

16. The vector of claim 15, wherein said cell type is selected from the group consisting of a cancer cell and a cell infected by an infectious agent.

17. The vector of claim 1, wherein said heterologous **nucleic acid**

sequence is selected from the group consisting of a tetracycline response element, a GAL4 response element, a progesterone receptor response element, a glucocorticoid receptor response element, an immunoglobulin kappa light chain enhancer, an immunoglobulin heavy chain enhancer, an α-1-antitrypsin enhancer, a serum albumin enhancer, a chorionic gonadotropin α-chain enhancer, a chorionic gonadotropin β-chain enhancer, an IL-2 enhancer, an IL-2 receptor enhancer, and an **HIV** response element.

18. The vector of claim 1, wherein said heterologous **nucleic acid** sequence encodes a functional protein selected from the group consisting of a **cytotoxic** agent, an immunopotentiator, a **vaccine** antigen and functional equivalents thereof.

19. The vector of claim 1, wherein said heterologous **nucleic acid** sequence encodes a functional protein selected from the group consisting of a diphtheria toxin, a ricin toxin, a modeccin toxin, an abrin toxin, a Pseudomonas exotoxin, a shiga toxin, a pokeweed antiviral protein, α-amanitin, a ribosome inhibiting protein, an autonomous parvovirus nonstructural protein, HSV thymidine kinase, and functional equivalents thereof.

20. The vector of claim 1, wherein said heterologous **nucleic acid** sequence encodes a functional protein selected from the group consisting of a diphtheria A-chain toxin, an autonomous parvovirus NS1 protein, HSV thymidine kinase, and functional equivalents thereof.

21. The vector of claim 1, wherein said heterologous **nucleic acid** sequence encodes a functional RNA selected from the group consisting of an antisense RNA, a ribozyme, and an RNA-based drug.

22. The vector of claim 1, wherein said heterologous **nucleic acid** sequence encodes a marker protein.

23. The vector of claim 1, wherein said parvovirus **nucleic acid** sequences comprise the terminal repeats of said parvovirus and at least one transcription control sequence selected from the group consisting of a transcription control sequence that regulates the expression of autonomous parvovirus nonstructural polypeptide genes and a transcription control sequence that regulates the expression of autonomous parvovirus structural polypeptide genes.

24. The vector of claim 1, wherein said heterologous **nucleic acid** sequences replace autonomous parvovirus sequences from about nucleotide 265 to about nucleotide 4530, wherein said heterologous sequences share substantial homology with LUIII.

25. The vector of claim 1, wherein said heterologous **nucleic acid** sequences replace autonomous parvovirus sequences from about nucleotide 145 to about nucleotide 4677, wherein said heterologeous sequences share substantial homology with LUIII.

26. The vector of claim 1 wherein introduction of said vector into a host cell effects transient gene transfer of said heterologous coding region into said cell.

27. The vector of claim 2, wherein said heterologous control element comprises a cancer cell-selective response element, wherein said heterologous coding region encodes a **cytotoxic** agent, and wherein said vector upon introduction into a host cancer cell inhibits cancer cell growth.

28. The vector of claim 1, wherein said vector comprises a single stranded **DNA** molecule.

29. The vector of claim 1, wherein said vector comprises a double

stranded **DNA** plasmid.

30. The vector of claim 1, wherein said vector is selected from the group consisting of pGLuLUCΔSV and pTOLuLUC.

31. The vector of claim 1, wherein said vector self-amplifies when provided with viral non-structural proteins by genetically-transformed host cell.

32. The vector of claim 1, wherein said vector is self-amplification incompetent.

33. The vector of claim 1, wherein said vector is self-packaging when provided with vector-packaging proteins by a genetically-transformed host cell.

34. The vector of claim 1, wherein said vector is self-packaging incompetent.

35. A recombinant virus particle comprising a recombinant vector packaged in an autonomous marvovirus capsid, said vector comprising **nucleic acid** sequences of an autonomous parvovirus joined to at least one heterologous **nucleic acid** sequence, said autonomous parvovirus **nucleic acid** sequences comprising functional left and right end inverted terminal repeats, said heterologous **nucleic acid** sequence being located between and operably linked to said **nucleic acid** sequences comprising said left and right inverted terminal repeats, wherein said vector is in a non-integrating form when transferred into a cell.

36. A recombinant virus particle comprising a recombinant vector packaged in an autonomous parvovirus capsid, said vector comprising **nucleic acid** sequences of an autonomous parvovirus joined to at least one heterologous **nucleic acid** sequence, said autonomous parvovirus **nucleic acid** sequences comprising functional left and right end inverted terminal repeats, said heterologous **nucleic acid** sequence being located between and operably linked to said **nucleic acid** sequences comprising said left and right inverted terminal repeats, said vector being in a non-integrating form within a cell after in vitro transfer of said vector.

37. The virus particle of claim 36, wherein said heterologous **nucleic acid** sequence is selected from the group consisting of a heterologous control element and a heterologous coding region.

38. The virus particle of claim 37, wherein said parvovirus **nucleic acid** sequences are selected from the group consisting of LuIII parvovirus, minute virus of mice, hamster parvovirus, feline panleukopenia virus, canine parvovirus, porcine parvovirus, latent rat virus, mink enteritis virus, human parvovirus, bovine parvovirus, and Aleutian mink disease parvovirus **nucleic acid** sequences.

39. The virus particle of claim 36, wherein said parvovirus **nucleic acid** sequences comprise a LuIII **nucleic acid** sequence.

40. The virus particle of claim 36, wherein said capsid is selected from the group consisting of LuIII parvovirus, minute virus of mice, hamster parvovirus, feline panleukopenia virus, canine parvovirus, porcine parvovirus, latent rat virus, mink enteritis virus, human parvovirus, bovine parvovirus, and Aleutian mink disease parvovirus **nucleic acid** sequences.

41. The virus particle of claim 36, wherein said capsid is selected from the group consisting of LuIII parvoVirus, minute virus of mice MVMi, minute virus of mice MVMp, and hamster parvovirus H1 capsids.

42. The virus particle of claim 36, wherein said capsid comprises a LuIII capsid.

43. The virus particle of claim 36, wherein said recombinant-vector is pseudotyped such that said vector is packaged in a capsid of a virus species other than the species of said parvovirus **nucleic acid** sequence.

44. The virus particle of claim 36, wherein said parvovirus **nucleic acid** sequences comprise a LuIII **nucleic acid** sequence and wherein said virus capsid is selected from the group consisting of LuIII parvovirus, minute virus of mice, hamster parvovirus, feline panleukopenia virus, canine parvovirus, porcine parvovirus, latent rat virus, and mink enteritis virus capsids.

45. The virus particle of claim 36, wherein said parvovirus **nucleic acid** sequences comprise a LuIII **nucleic acid** sequence and wherein said virus capsid is selected from the group consisting of LuIII parvovirus, minute virus of mice MVMi, minute virus of mice MVMp, and hamster parvovirus H1 capsids.

46. The virus particle of claim 36, wherein infection of said virus particle into a host cell effects transient gene transfer of said heterologous coding region into said cell.

47. The virus particle of claim 37, wherein said heterologous control element comprises a cancer cell-selective response element, wherein said heterologous coding region encodes a **cytotoxic** agent, and wherein infection of said virus particle into a host cancer cell inhibits cancer cell growth.

48. A gene delivery vehicle comprising a recombinant vector comprising **nucleic acid** sequences of an autonomous parvovirus joined to at least one heterologous **nucleic acid** sequence, said autonomous parvovirus **nucleic acid** sequences comprising functional left and right end inverted terminal repeats, said heterologous **nucleic acid** sequence being located between and operably linked to said **nucleic acid** sequences comprising said left and right inverted terminal repeats, wherein said vector is in a non-integrating form when transferred into a cell.

49. The virus particle of claim 36, wherein said particle exhibits characteristics of an autonomous parvovirus, said characteristics comprising high stability, lack of integration, high titer, and maintenance of infectivity upon concentration.

50. A gene delivery vehicle comprising a recombinant vector comprising **nucleic acid** sequences of an autonomous parvovirus joined to at least one heterologous **nucleic acid** sequence, said autonomous parvovirus **nucleic acid** sequences comprising functional left and right end inverted terminal repeats, said heterologous **nucleic acid** sequence being located between and operably linked to said **nucleic acid** sequences comprising said left and right inverted terminal repeat, said vector being in a non-integrating form within a cell after in vitro transfer of said vector.

51. The gene delivery vehicle of claim 50, wherein said vector is packaged in an autonomous parvovirus capsid to form a recombinant virus particle effective to deliver said vector to said host cell.

52. The gene delivery vehicle of claim 51, wherein said capsid targets said virus particle to a selected population of host cells.

53. The gene delivery vehicle of claim 50, wherein said vector is attached to a carrier effective to deliver said vector to said host cell.

54. The gene delivery vehicle of claim 53, wherein said carrier is selected from the group consisting of liposomes and viruses.

55. The gene delivery vehicle of claim 52, wherein said heterologous **nucleic acid** sequence comprises a control element which is operably linked to a coding region, which control element is selectively functional in a particular population of cells and selectively directs expression of said coding region in said cell population.

56. The gene delivery vehicle of claim 50, wherein said heterologous **nucleic acid** sequence encodes an RNA or protein for treating said host cell.

57. The gene delivery vehicle of claim 50, wherein said vehicle upon introduction into said host cell is capable of substantially destroying a selected population of host cells, said heterologous **nucleic acid** sequence comprising a heterologous response element that is selectively expressed by said cell population, said response element being operatively linked to a promoter and to a coding region capable of encoding a compound that is substantially **cytotoxic** to said cell population.

58. The gene delivery vehicle of claim 57, wherein said compound is selected from the group consisting of a diphtheria toxin, an autonomous parvovirus NS1 protein, and HSV thymidine kinase.

59. A recombinant **nucleic acid** comprising **nucleic acid** sequences of an autonomous parvovirus joined to a heterologous **nucleic acid** sequence comprising a heterologous control element or heterologous coding region, said autonomous parvovirus **nucleic acid** sequences comprising functional left and right end inverted terminal repeats, said heterologous **nucleic acid** sequence being located between and operably linked to said **nucleic acid** sequences comprising said left and right inverted terminal repeats, wherein said recombinant **nucleic acid** is in a non-integrating form when transferred into a cell.

60. The gene delivery vehicle of claim 50, wherein said heterologous **nucleic acid** sequence restores the function of a defective gene in said host cell.

61. A recombinant **nucleic acid** comprising **nucleic acid** sequences of an autonomous parvovirus joined to a heterologous **nucleic acid** sequence comprising a heterologous control element or heterologous coding region, said autonomous parvovirus **nucleic acid** sequences comprising functional left and right end inverted terminal repeats, said heterologous **nucleic acid** sequence being located between and operably linked to said **nucleic acid** sequences comprising said left and right inverted terminal repeats, said recombinant **nucleic acid** being in a non-integrating form within a cell after in vitro transfer of said recombinant **nucleic acid**.

62. The recombinant **nucleic acid** of claim 61, wherein said heterologous **nucleic acid** sequence comprises a heterologous control element operatively linked to a heterologous coding region.

63. The autonomous parvovirus helper construct pSVLu.

64. A non-integrating vector comprising **nucleic acid** sequences of an autonomous parvovirus joined to at least one heterologous **nucleic acid** sequence, the expression of which is regulated by a control element, said autonomous parvovirus **nucleic acid** sequences comprising functional left and right end inverted terminal repeats, said heterologous **nucleic acid** sequence being located between and operably linked to said **nucleic acid** sequences comprising said left and right inverted terminal repeats, said autonomous parvovirus **nucleic acid** sequences being devoid of **nucleic acid** sequences

encoding either structural or nonstructural autonomous parvovirus polypeptides.

65. The vector of claim 64, wherein said vector is packaged within an autonomous parvovirus capsid that target selected cell types.

66. The vector of claim 64, wherein said vector is capable of effecting transient expression of said heterologous **nucleic acid** sequence in a host cell.

67. A method for transferring a heterologous **nucleic acid** sequence into a host cell in vitro comprising introducing into said cell a recombinant vector comprising **nucleic acid** sequences of an autonomous parvovirus joined to at least one heterologous **nucleic acid** sequence selected from the group consisting of a heterologous control element and a heterologous coding region, said autonomous parvovirus **nucleic acid** sequences comprising functional left and right end inverted terminal repeats, said heterologous **nucleic acid** sequence being located between and operably linked to said **nucleic acid** sequences comprising said left and right inverted terminal repeats, wherein said vector is in a non-integrating form when transferred into a cell.

68. The vector of claim 67, wherein expression of said **cytotoxic** agent is sufficient to destroy selected cell types.

69. A method for transferring a heterologous **nucleic acid** sequence into a host cell in vitro comprising introducing into said cell a recombinant vector comprising **nucleic acid** sequences of an autonomous parvovirus joined to at least one heterologous **nucleic acid** sequence selected from the group consisting of a heterologous control element and a heterologous coding region, said autonomous parvovirus **nucleic acid** sequences comprising functional left and right end inverted terminal repeats, said heterologous **nucleic acid** sequence being located between and operably linked to said **nucleic acid** sequences comprising said left and right inverted terminal repeats, said vector being in a non-integrating form within a cell after in vitro transfer of said vector.

70. A method for transferring a heterologous **nucleic acid** sequence into a cell in vitro comprising infecting said cell with a recombinant virus particle comprising a recombinant vector packaged in an autonomous parvovirus capsid, said vector comprising **nucleic acid** sequences of an autonomous parvovirus joined to at least one heterologous **nucleic acid** sequence selected from the group consisting of a heterologous control element and a heterologous coding region, said autonomous parvovirus **nucleic acid** sequences comprising functional left and right end inverted terminal repeats, said heterologous **nucleic acid** sequence being located between and operably linked to said **nucleic acid** sequences comprising said left and right inverted terminal repeats, wherein said vector is in a non-integrating form when transferred into a cell.

71. A method for substantially destroying a selected population of cells comprising administering to an in vitro cell population at least one recombinant vector comprising autonomous parvovirus **nucleic acid** sequences joined to at least one heterologous **nucleic acid** sequence having a heterologous response element that is selectively functional in said cell population, said response element being operably linked to a promoter and to a coding region encoding a compound that is substantially **cytotoxic** to said cell population, said autonomous parvovirus **nucleic acid** sequences comprising functional left and right end inverted terminal repeats, said heterologous **nucleic acid** sequence being located between and operably linked to said **nucleic acid** sequences comprising said left and right inverted terminal repeats, wherein said vector is in a non-integrating form when

transfected into a cell.

72. A method for transferring a heterologous **nucleic acid** sequence into a cell in vitro comprising infecting said cell with a recombinant virus particle comprising a recombinant vector packaged in an autonomous parvovirus capsid, said vector comprising **nucleic acid** sequences of an autonomous parvovirus joined to at least one heterologous **nucleic acid** sequence selected from the group consisting of a heterologous control element and a heterologous coding region, said autonomous parvovirus **nucleic acid** sequences comprising functional left and right end inverted terminal repeats, said heterologous **nucleic acid** sequence being located between and operably linked to said **nucleic acid** sequences comprising said left and right inverted terminal repeats, said vector being in a non-integrating form within a cell after in vitro transfer of said vector.

73. A method for substantially destroying a selected population of cells comprising administering to an in vitro cell population at least one recombinant vector comprising autonomous parvovirus **nucleic acid** sequences joined to at least one heterologous **nucleic acid** sequence having a heterologous response element that is selectively functional in said cell population, said response element being operably linked to a promoter and to a coding region encoding a compound that is substantially **cytotoxic** to said cell population, said autonomous parvovirus **nucleic acid** sequences comprising functional left and right end inverted terminal repeats, said heterologous **nucleic acid** sequence being located between and operably linked to said **nucleic acid** sequences comprising said left and right inverted terminal repeats, said vector being in a non-integrating form within a cell after in vitro transfer of said vector.

74. The method of claim 73, wherein said coding region encodes an antisense RNA, a ribozyme, an RNA-based drug, or a **cytotoxic** protein.

75. The method of claim 73, wherein said selected population of cells comprise cancer cells or cells infected with an infectious agent.

76. A method for producing a recombinant virus particle useful in the delivery of a gone to a targeted cell, comprising: (a) co-transfecting a host cell in vitro with a recombinant non-integrating vector comprising acid sequences of an autonomous parvovirus joined to at least one heterologous **nucleic acid** sequence and with a helper construct that effects at least one function selected from the group consisting of amplification of said vector and packaging of said vector in a parvovirus capsid, said autonomous parvovirus **nucleic acid** sequences comprising functional left and right end inverted terminal repeats, said heterologous **nucleic acid** sequence being located between and operably linked to said **nucleic acid** sequences comprising said left and right inverted terminal repeats; and (b) culturing said transfected host cell in an effective medium to produce a recombinant virus particle said vector being in a non-integrating form within a cell after in vitro transfer of said vector.

77. The method of claim 76 wherein said helper construct is pSVLu.

78. A method for producing a heterologous product selected from the group consisting of RNA products and protein products comprising: (a) transfecting a host cell in vitro with a recombinant non-integrating vector comprising **nucleic acid** sequences of an autonomous parvovirus joined to at least one heterologous **nucleic acid** sequence encoding said product, said autonomous parvovirus **nucleic acid** sequences comprising functional left and right inverted terminal repeats, said heterologous **nucleic acid** sequence being located between and operably linked to said **nucleic acid** sequences comprising said left and right inverted terminal repeats; and (b) culturing said transfected host cell in an effective medium to produce said product.

79. The method of claim 78, wherein said host cell is further transfected with a helper construct that effects replication of said vector.

80. A recombinant vector comprising **nucleic acid** sequences of an autonomous parvovirus joined to at least one heterologous **nucleic acid** sequence, said autonomous parvovirus **nucleic acid** sequences comprising functional left and right end inverted terminal repeats, said heterologous **nucleic acid** sequence being located between and operably linked to said **nucleic acid** sequences comprising said left and right inverted terminal repeats.

81. A recombinant virus particle comprising a recombinant vector packaged in an autonomous parvovirus capsid, said vector comprising autonomous parvovirus **nucleic acid** sequences joined to at least one heterologous **nucleic acid** sequence, said autonomous parvovirus **nucleic acid** sequences comprising functional left and right end inverted terminal repeats, said heterologous **nucleic acid** sequence being located between and operably linked to said **nucleic acid** sequences comprising said left and right inverted terminal repeats.

82. A gene delivery vehicle comprising a recombinant vector comprising autonomous parvovirus **nucleic acid** sequences joined to at least one heterologous **nucleic acid** sequence, said autonomous parvovirus **nucleic acid** sequences comprising functional left and right end inverted terminal repeats, said heterologous **nucleic acid** sequence being located between and operably linked to said **nucleic acid** sequences comprising said left and right inverted terminal repeats.

83. A recombinant **nucleic acid** comprising autonomous parvovirus **nucleic acid** sequences joined to a heterologous **nucleic acid** sequence comprising a heterologous control element or a heterologous coding region, said autonomous parvovirus **nucleic acid** sequences comprising functional left and right end inverted terminal repeats, said heterologous **nucleic acid** sequence being located between and operably linked to said **nucleic acid** sequences comprising said left and right inverted terminal repeats.

L27 ANSWER 33 OF 33 USPATFULL on STN
96:96943 **HIV**-3 retrovirus and its use.
De Leys, Robert, Grimbergen, Belgium
Vanderborght, Bart, Geel, Belgium
Saman, Eric, Niklaas, Belgium
Van Heuverswyn, Hugo, Laarne, Belgium
Innogenetics N.V., Belgium (non-U.S. corporation)
US 5567603 19961022
APPLICATION: US 1994-228519 19940415 (8) <--
PRIORITY: EP 1988-109200 19880609
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Described is a new retrovirus designated **HIV**-3, samples of which have been deposited in the European Collection of Animal Cell Cultures (ECACC) under V88060301. The morphological and immunological properties exhibited by the **HIV**-3 retrovirus class include:

a diameter of approximately 120 nm; a tropism for T4 lymphocytes; cultivation in T4 receptor-bearing immortalized cell lines; cytotoxicity for the lymphocytes that it infects; a magnesium dependent reverse transcriptase activity;

the genomic RNA of **HIV**-3 hybridizes neither with the sequences of **HIV**-1 nor with the sequences of **HIV**-2 under stringent hybridization conditions;

lysates of the virus contain a p25 protein which is immunologically distinct from the p19 protein of HTLV-I and the p24 proteins of **HIV**-1 and **HIV**-2 as determined by Western blot analysis, respectively;

lysates of the virus contain a gp120 protein which is immunologically distinct from the gp110 protein of HTLV-I, the gp120 of **HIV**-1 and the gp120 of **HIV**-2 as determined by Western blot analysis;

the lysate of the virus contains in addition a gp41 glycoprotein with a molecular weight of 40,000-45,000; and

lysates of the virus contain a p12 protein which is immunologically distinct from the p12 proteins of **HIV**-1 and **HIV**-2 as determined by Western blot analysis.

Also described are nucleic acid sequences derived from **HIV**-3 RNA which can be used as hybridization probes to detect the presence of **HIV**-3 virus.

CLM What is claimed is:

1. **HIV**-3 retrovirus or variants of this virus having the essential morphological and immunological properties of any of the retroviruses deposited at the European Collection of Animal Cell Cultures (ECACC) under No. V88060301, said essential morphological and immunological properties are as follows: the virus exhibits a tropism for T4 lymphocytes; the virus is **cytotoxic** for the lymphocytes that it infects; the virus has a diameter of approximately 120 nm; the virus possesses a magnesium dependent reverse transcriptase activity; the virus can be cultivated in T4 receptor-bearing immortalized cell lines; lysates of the virus contain a p25 protein which is immunologically distinct from the p19 protein of HTLV-I and the p24 proteins of **HIV**-1 and **HIV**-2 as determined by Western blot analysis, respectively; lysates of the virus contain a gp120 protein which is immunologically distinct from the gp110 protein of HTLV-I, the gp120 of **HIV**-1 and the gp120 of **HIV**-2 as determined by western blot analysis; the lysate of the virus contains in addition a gp41 glycoprotein with a molecular weight of 40,000-45,000; the genomic RNA of **HIV**-3 hybridizes neither with the sequences of **HIV**-1 nor with the sequences of **HIV**-2 under stringent hybridization conditions; and lysates of the virus contain a p12 protein which is immunologically distinct from the p12 proteins of **HIV**-1 and **HIV**-2 as determined by Western blot analysis.

2. The retrovirus of claim 1 characterized in that its RNA virtually hybridizes neither with the Env gene and the LTR close to it of **HIV**-1, in particular not with the nucleotide sequence 8352-9538 of **HIV**-1, nor with the sequences of the Pol region of the **HIV**-1 genome under stringent conditions.

3. A process for the production of the retrovirus of claim 1 characterized by culturing human T4 lymphocytes, or permanent cell lines derived therefrom carrying the T4 phenotype, with lymphocytes or cell lines that have previously been infected with an isolate of said retrovirus, as well as recovering and purifying the retrovirus from the culture medium.

4. A process for the production of any of the proteins or glycoproteins p12, p16, p25, gp41 and gp120 of the retrovirus of claim 1 comprising: inserting the corresponding **nucleic acid** sequence of said retrovirus in an expression vector, transforming a host with said vector, culturing the transformed host as well as recovering and purifying the expressed protein.

5. The retrovirus of claim 1 having genomic RNA which hybridizes neither with the sequences of **HIV**-1 nor with the sequences of **HIV**-2 under stringent hybridization conditions, said genomic RNA comprising an LTR region also comprises a nucleotide sequence which hybridizes under stringent conditions with the following nucleotide sequence:

10 20 30 40 50 60

CCCATGGATT
TGAAGATACA
CATAAAGAAA
TACTGATGTG
GAAGTTTGAT
AGATCTCTAG

70 80 90 100 110 120

GCAACACCCA
TGTTGCTATG
ATAACTCACC
CAGAGCTCTT
CCAGAAGGAC
TAAAAACTGC

130 140 150 160 170 180

TGACCTGAAG
ATTGCTGACA
CTGTGGAACT
TTCCAGCAAA
GACTGCTGAC
ACTGCGGGGA

190 200 210 220 230 240

CTTTCCAGTG
GGAGGGACAG
GGGGCGGTTC
GGGGAGTGGC
TAACCCTCAG
AAGCTGCATA

250 260 270 280 290 300

TAAGCAGCCG
CTTTCTGCTT
GTACCGGGTC
TCGGTTAGAG
GACCAGGTCT
GAGCCCGGGA

310 320 330 340 350 360

GCTCCCTGGC
CTCTAGCTGA
ACCCGCTCGT
TAACGCTCAA
TAAAGCTTGC
CTTGAGTGAG

A.

6. The retrovirus of claim 1 having genomic RNA which hybridizes neither with sequences of **HIV**-1 nor with the sequences of **HIV**-2 under stringent hybridization conditions, said genomic RNA also comprises a nucleotide sequence which hybridizes under stringent conditions with the following nucleotide sequence:

10 20 30 40 50 60

AACATGGGAA ACGCATTGAG
AAAAGGTAAA
TTTGAGGGAT GGGCAGCAGT
AAGAGAAAGA

70 80 90 100 110 120

ATGAGAAGAA CTAGAACTTT
CCCTGAGTCT
GAACCATGCG CACCTGGAGT
AGGACAGATC

130 140 150 160 170 180

TCCAGGGAAT TAGCAGCTAG
AGGAGGGATA
CCAAGTTCCC ATACTCCTCA
AAACAATGCA

190 200 210 220 230 240
GCCCTTGCAT TCCTAGAAAG
TCACCAAGAG
GAAGAAGTAG GTTTTCCAGT
AGCACCTCAA

250 260 270 280 290 300
GTGCCTCTAA GGCCAATGAC
CTATAAAGGA
GCATTTGACC TCAGCTTCTT
TTTAAAAGAA

310 320 330 340 350 360
AAGGGAGGAC TGGAAGGGTT
AATTTACTCC
CATAAAAGAG CAGAAATCCT
GGATCTTTGG

GTGTATAA.

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7. A nucleotide sequence comprising the entire genomic RNA of the retrovirus of claim 1.

8. A nucleotide sequence comprising cDNA corresponding to the entire genomic RNA of the retrovirus of claim 1.

9. A nucleotide sequence coding for the amino__ acid sequences of proteins p12, p16 or p25 of the retrovirus of claim 1.

10. A nucleotide sequence coding for the amino__ acid sequences of glycoproteins gp41 or gp120 of the retrovirus of claim 1.

11. A process for the production of a hybridization probe for the detection of the RNA of the retrovirus of claim 1 comprising: inserting a nucleotide sequence of any of claims 7 to 10 in a cloning vector by in vitro recombination, cloning the modified vector obtained in a suitable cellular host, and recovering the hybridization probe.

12. The nucleotide sequence of any one of claims 7 to 10 which is labelled.

13. A recombinant **nucleic acid** vector comprising a nucleotide sequence of any one of claims 7 to 10 inserted therein.

14. The retrovirus of claim 1 wherein the LTR sequence of said retrovirus is about 70% or less homologous to the LTR sequence of **HIV**-1 or **HIV**-2.

15. A nucleotide sequence identified by the sequence:

---

10 20 30 40 50 60
CCCATGGATT TGAAGATACA
CATAAAGAAA TACTGATGTG
GAAGTTTGAT
AGATCTCTAG

70 80 90 100 110 120
GCAACACCCA TGTTGCTATG
ATAACTCACC CAGAGCTCTT
CCAGAAGGAC
TAAAAACTGC

130 140 150 160 170 180

TGACCTGAAG ATTGCTGACA
CTGTGGAACT TTCCAGCAAA
GACTGCTGAC
ACTGCGGGGA

190 200 210 220 230 240
CTTTCCAGTG GGAGGGACAG
GGGGCGGTTC GGGGAGTGGC
TAACCCTCAG
AAGCTGCATA

250 260 270 280 290 300
TAAGCAGCCG CTTTCTGCTT
GTACCGGGTC TCGGTTAGAG
GACCAGGTCT
GAGCCCGGGA

310 320 330 340 350 360
GCTCCCTGGC CTCTAGCTGA
ACCCGCTCGT TAACGCTCAA
TAAAGCTTGC
CTTGAGTGAG

A;
or
10 20 30 40 50 60
AACATGGGAA ACGCATTGAG
AAAAGGTAAA TTTGAGGGAT
GGGCAGCAGT
AAGAGAAAGA

70 80 90 100 110 120
ATGAGAAGAA CTAGAACTTT
CCCTGAGTCT GAACCATGCG
CACCTGGAGT
AGGACAGATC

130 140 150 160 170 180
TCCAGGGAAT TAGCAGCTAG
AGGAGGGATA CCAAGTTCCC
ATACTCCTCA
AAACAATGCA

190 200 210 220 230 240
GCCCTTGCAT TCCTAGAAAG
TCACCAAGAG GAAGAAGTAG
GTTTTCCAGT
AGCACCTCAA

250 260 270 280 290 300
GTGCCTCTAA GGCCAATGAC
CTATAAAGGA GCATTTGACC
TCAGCTTCTT
TTTAAAAGAA

310 320 330 340 350 360
AAGGGAGGAC TGGAAGGGTT
AATTTACTCC CATAAAAGAG
CAGAAATCCT
GGATCTTTGG

GTGTATAA.

=> d his

(FILE 'HOME' ENTERED AT 19:42:02 ON 01 APR 2004)

FILE 'USPATFULL' ENTERED AT 19:42:32 ON 01 APR 2004
E FRANCHINI GENOVEFFA/IN
L1 7 S E3
L2 0 S ZDENEK HEL/IN

```
                E ZDENEK HEL/IN
L3            0 S HEL ZDENEK/IN S HEL ZDENEK/IN
L4            0 S GENE SHEARER/IN
L5            1 S SHEARER GENE/IN
                E SHEARER GENE/IN
L6            7 S E4
                E NACSA JANOS/IN

     FILE 'MEDLINE' ENTERED AT 19:47:38 ON 01 APR 2004
                E FRANCHINI G/AU
L7          196 S E3 OR E4
L8           67 S L7 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L9           16 S L8 AND (MHC OR MAJOR HISTOCOMPATIBILITY OR CTL OR CYTOTOXIC T
L10           0 S HEL Z/AU S HEL Z/AU
                E SHEARER G M/AU
L11         358 S E3 OR E6 OR E7
L12         118 S L11 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L13          20 S L12 AND (MAJOR HISTOCOMPATIBILITY OR CTL OR CYTOTOXIC)
                E NACSA J/AU
L14          22 S E3 OR E4

     FILE 'WPIDS' ENTERED AT 20:01:20 ON 01 APR 2004
                E FRANCHINI G/IN
L15          18 S E3
L16          10 S L15 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
                E SHEARER G M/IN
L17          10 S E3
L18          15 S E3 OR E2
                E NACSA J/IN
L19           3 S E3

     FILE 'USPATFULL' ENTERED AT 20:09:31 ON 01 APR 2004
L20       31746 S (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L21       10927 S L20 AND (CTL OR CYTOTOXIC)
L22        1761 S L21 AND (HIV/CLM OR HUMAN IMMUNODEFICIENCY VIRUS/CLM)
L23         233 S L22 AND (CTL/CLM OR CYTOTOXIC/CLM)
L24         186 S L23 AND (VACCIN? OR IMMUNOGEN?)
L25         182 S L24 AND (PROTECT? OR PREVENT?)
L26          96 S L25 AND (DNA/CLM OR NUCLEIC ACID/CLM)
L27          33 S L26 AND AY<2000

=> s us6656471/pn
L28           1 US6656471/PN

=> d l28,exnam

L28  ANSWER 1 OF 1  USPATFULL on STN
EXNAM  Primary Examiner: Stucker, Jeffrey


=> s us6319666/pn
L29           1 US6319666/PN

=> d l29,exnam

L29  ANSWER 1 OF 1  USPATFULL on STN
EXNAM  Primary Examiner: Park, Hankyel T.


=> d his

     (FILE 'HOME' ENTERED AT 19:42:02 ON 01 APR 2004)

     FILE 'USPATFULL' ENTERED AT 19:42:32 ON 01 APR 2004
                E FRANCHINI GENOVEFFA/IN
L1            7 S E3
```

```
L2              0 S ZDENEK HEL/IN
                  E ZDENEK HEL/IN
L3              0 S HEL ZDENEK/IN S HEL ZDENEK/IN
L4              0 S GENE SHEARER/IN
L5              1 S SHEARER GENE/IN
                  E SHEARER GENE/IN
L6              7 S E4
                  E NACSA JANOS/IN

     FILE 'MEDLINE' ENTERED AT 19:47:38 ON 01 APR 2004
                  E FRANCHINI G/AU
L7            196 S E3 OR E4
L8             67 S L7 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L9             16 S L8 AND (MHC OR MAJOR HISTOCOMPATIBILITY OR CTL OR CYTOTOXIC T
L10             0 S HEL Z/AU S HEL Z/AU
                  E SHEARER G M/AU
L11           358 S E3 OR E6 OR E7
L12           118 S L11 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L13            20 S L12 AND (MAJOR HISTOCOMPATIBILITY OR CTL OR CYTOTOXIC)
                  E NACSA J/AU
L14            22 S E3 OR E4

     FILE 'WPIDS' ENTERED AT 20:01:20 ON 01 APR 2004
                  E FRANCHINI G/IN
L15            18 S E3
L16            10 S L15 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
                  E SHEARER G M/IN
L17            10 S E3
L18            15 S E3 OR E2
                  E NACSA J/IN
L19             3 S E3

     FILE 'USPATFULL' ENTERED AT 20:09:31 ON 01 APR 2004
L20         31746 S (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L21         10927 S L20 AND (CTL OR CYTOTOXIC)
L22          1761 S L21 AND (HIV/CLM OR HUMAN IMMUNODEFICIENCY VIRUS/CLM)
L23           233 S L22 AND (CTL/CLM OR CYTOTOXIC/CLM)
L24           186 S L23 AND (VACCIN? OR IMMUNOGEN?)
L25           182 S L24 AND (PROTECT? OR PREVENT?)
L26            96 S L25 AND (DNA/CLM OR NUCLEIC ACID/CLM)
L27            33 S L26 AND AY<2000
L28             1 S US6656471/PN
L29             1 S US6319666/PN

=> file medline
COST IN U.S. DOLLARS                              SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                   183.34     368.43

FILE 'MEDLINE' ENTERED AT 20:22:25 ON 01 APR 2004

FILE LAST UPDATED: 1 APR 2004 (20040401/UP).  FILE COVERS 1951 TO DATE.

On February 29, 2004, the 2004 MeSH terms were loaded.  See HELP RLOAD
for details. OLDMEDLINE now back to 1951.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
MeSH 2004 vocabulary.  See http://www.nlm.nih.gov/mesh/ and
http://www.nlm.nih.gov/pubs/techbull/nd03/nd03_mesh.html for a
description of changes.

This file contains CAS Registry Numbers for easy and accurate
substance identification.

=> s (HIV or human immunodeficiency virus)
        135256 HIV
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84047 84 HUMAN
112466 IMMUNODEFICIENCY
372233 VIRUS
42485 HUMAN IMMUNODEFICIENCY VIRUS
(HUMAN(W)IMMUNODEFICIENCY(W)VIRUS)
L30 139974 (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)

=> s l30 and (CTL or cytotoxic T cell? or cytotoxic T lymphocyte? or CD8)
11061 CTL
81352 CYTOTOXIC
3621943 T
2479333 CELL?
6698 CYTOTOXIC T CELL?
(CYTOTOXIC(W)T(W)CELL?)
81352 CYTOTOXIC
3621943 T
357886 LYMPHOCYTE?
11810 CYTOTOXIC T LYMPHOCYTE?
(CYTOTOXIC(W)T(W)LYMPHOCYTE?)
36909 CD8
L31 5709 L30 AND (CTL OR CYTOTOXIC T CELL? OR CYTOTOXIC T LYMPHOCYTE? OR CD8)

=> s l31 and (escape or evasion)
16126 ESCAPE
1442 EVASION
L32 176 L31 AND (ESCAPE OR EVASION)

=> s l32 and (vaccin? or prevent? or therap?)
145642 VACCIN?
874124 PREVENT?
2521140 THERAP?
L33 78 L32 AND (VACCIN? OR PREVENT? OR THERAP?)

=> d l33,cbib,ab,1-78

L33 ANSWER 1 OF 78 MEDLINE on STN
2004144790. PubMed ID: 15036041. **CTL** ontogeny and viral **escape**: implications for **HIV**-1 **vaccine** design. Yang Otto O. (Division of Infectious Diseases/Department of Medicine, UCLA Medical Center, 37-121 Center for Health Sciences, 10833 LeConte Avenue, Los Angeles, CA 90095, USA.. oyang@mednet.ucla.edu) . Trends in immunology, (2004 Mar) 25 (3) 138-42. Journal code: 100966032. ISSN: 1471-4906. Pub. country: England: United Kingdom. Language: English.

L33 ANSWER 2 OF 78 MEDLINE on STN
2004101212. PubMed ID: 14966520. Reversion of **CTL escape**-variant immunodeficiency viruses in vivo. Friedrich Thomas C; Dodds Elizabeth J; Yant Levi J; Vojnov Lara; Rudersdorf Richard; Cullen Candice; Evans David T; Desrosiers Ronald C; Mothe Bianca R; Sidney John; Sette Alessandro; Kunstman Kevin; Wolinsky Steven; Piatak Michael; Lifson Jeffrey; Hughes Austin L; Wilson Nancy; O'Connor David H; Watkins David I. (Wisconsin National Primate Research Center, Madison, Wisconsin 53715, USA.) Nature medicine, (2004 Mar) 10 (3) 275-81. Journal code: 9502015. ISSN: 1078-8956. Pub. country: United States. Language: English.

AB Engendering **cytotoxic T-lymphocyte** (**CTL**) responses is likely to be an important goal of **HIV vaccines**. However, CTLs select for viral variants that **escape** immune detection. Maintenance of such **escape** variants in human populations could pose an obstacle to **HIV vaccine** development. We first observed that **escape** mutations in a heterogeneous simian immunodeficiency virus (SIV) isolate were lost upon passage to new animals. We therefore infected macaques with a cloned SIV bearing **escape** mutations in three immunodominant **CTL** epitopes, and followed viral evolution after infection. Here we show that each mutant epitope sequence continued to evolve in vivo, often re-establishing the original, **CTL**-susceptible sequence. We conclude that **escape** from **CTL**

responses may exact a cost to viral fitness. In the absence of selective pressure upon transmission to new hosts, these original **escape** mutations can be lost. This suggests that some **HIV CTL** epitopes will be maintained in human populations.

L33 ANSWER 3 OF 78 MEDLINE on STN
2004084894. PubMed ID: 14769905. Cell-mediated immune responses in healthy children with a history of subclinical infection with Japanese encephalitis virus: analysis of CD4+ and **CD8**+ T cell target specificities by intracellular delivery of viral proteins using the **human immunodeficiency virus** Tat protein transduction domain. Kumar Priti; Krishna Venkatramana D; Sulochana Paramadevanapalli; Nirmala Gejjehalli; Haridattatreya Maganti; Satchidanandam Vijaya. (Department of Microbiology and Cell Biology, Indian Institute of Science, Bangalore, Karnataka 560012, India.) Journal of general virology, (2004 Feb) 85 (Pt 2) 471-82. Journal code: 0077340. ISSN: 0022-1317. Pub. country: England: United Kingdom. Language: English.

AB Japanese encephalitis virus (JEV), a single-stranded positive-sense RNA virus of the family Flaviviridae, is the major cause of paediatric encephalitis in Asia. The high incidence of subclinical infections in Japanese encephalitis-endemic areas and subsequent **evasion** of encephalitis points to the development of immune responses against JEV. Humoral responses play a central role in protection against JEV; however, cell-mediated immune responses contributing to this end are not fully understood. The structural envelope (E) protein, the major inducer of neutralizing antibodies, is a poor target for T cells in natural JEV infections. The extent to which JEV non-structural proteins are targeted by T cells in subclinically infected healthy children would help to elucidate the role of cell-mediated immunity in protection against JEV as well as other flaviviral infections. The property of the Tat peptide of **Human immunodeficiency virus** to transduce proteins across cell membranes, facilitating intracellular protein delivery following exogenous addition to cultured cells, prompted us to express the four largest proteins of JEV, comprising 71 % of the JEV genome coding sequence, as Tat fusions for enumerating the frequencies of virus-specific CD4(+) and **CD8**(+) T cells in JEV-immune donors. At least two epitopes recognized by distinct HLA alleles were found on each of the non-structural proteins, with dominant antiviral Th1 T cell responses to the NS3 protein in nearly 96 % of the cohort. The data presented here show that non-structural proteins are frequently targeted by T cells in natural JEV infections and may be efficacious supplements for the predominantly antibody-eliciting E-based JEV **vaccines**.

L33 ANSWER 4 OF 78 MEDLINE on STN
2004038290. PubMed ID: 14738219. **Vaccines** and **vaccine** strategies against **HIV**. Stratov Ivan; DeRose Robert; Purcell Damian F J; Kent Stephen J. (Department of Immunology and Microbiology, University of Melbourne, Victoria 3010, Australia.) Current drug targets, (2004 Jan) 5 (1) 71-88. Journal code: 100960531. ISSN: 1389-4501. Pub. country: Netherlands. Language: English.

AB The **HIV**/AIDS pandemic is a global emergency and a **preventive HIV vaccine** is urgently needed. **HIV** has, however, proved a difficult pathogen to **vaccinate** against. This is largely because **HIV** has a very high mutation rate and can **escape** immune responses, it has a latent stage where it can rest silently integrated into host DNA, and neutralising antibodies that can neutralise diverse field strains have so far proved difficult to induce. There is however, considerable evidence now that **HIV**-specific CD4 and **CD8** T cells can provide partial control of **HIV** replication and delay or **prevent** disease. Technologies to quantify and analyse **HIV**-specific T cells have advanced recently, and in particular ELISpot, intracellular cytokine staining and tetramer studies have provided clear analyses of the ability of **HIV vaccines** to induce T cell responses. The use of pools of overlapping **HIV** peptides as in vitro antigens has also provided a standardised reagent for accurate measurement of T cell responses. **HIV** protein **vaccines** have not induced broad neutralising antibodies or T cell responses and failed to

protect humans in the only phase III efficacy trial yet completed. Viral vectors, such as canarypox, engineered to express **HIV** genes, have induced **HIV**-specific **CD8** T cell responses in a minority of subjects in phase II trials and are proceeding to human efficacy trials. Currently, the most effective method of inducing **CD8+ CTL** immunity in non-human primates utilises priming with naked plasmid DNA and then boosting with recombinant viral vectors both encoding various parts of the **HIV** genome. Such **vaccines** have induced non-sterilising immunity to virulent Simian/**Human immunodeficiency virus** exposure in macaques and have entered phase I trials. Multiple other approaches are also being evaluated in what has become a global effort for a **vaccine** to **prevent** AIDS. Although an **HIV vaccine** is still a long way off, there is reason to be optimistic that a **vaccine** to **prevent** AIDS will eventually be developed.

L33 ANSWER 5 OF 78 MEDLINE on STN
2004023548. PubMed ID: 14722287. Impaired processing and presentation of **cytotoxic-T-lymphocyte** (**CTL**) epitopes are major **escape** mechanisms from **CTL** immune pressure in **human immunodeficiency virus** type 1 infection. Yokomaku Yoshiyuki; Miura Hideka; Tomiyama Hiroko; Kawana-Tachikawa Ai; Takiguchi Masafumi; Kojima Asato; Nagai Yoshiyuki; Iwamoto Aikichi; Matsuda Zene; Ariyoshi Koya. (AIDS Research Center, National Institute of Infectious Diseases, University of Tokyo, Tokyo, Japan.) Journal of virology, (2004 Feb) 78 (3) 1324-32. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Investigating **escape** mechanisms of **human immunodeficiency virus** type 1 (**HIV**-1) from **cytotoxic T lymphocytes** (CTLs) is essential for understanding the pathogenesis of **HIV**-1 infection and developing effective **vaccines**. To study the processing and presentation of known **CTL** epitopes, we prepared Epstein-Barr virus-transformed B cells that endogenously express the gag gene of six field isolates by adopting an env/nef-deletion **HIV**-1 vector pseudotyped with vesicular stomatitis virus G protein and then tested them for the recognition by Gag epitope-specific **CTL** lines or clones. We observed that two field variants, SLFNTVAVL and SVYNTVATL, of an A*0201-restricted Gag **CTL** epitope SLYNTVATL, and three field variants, KYRLKHLVW, QYRLKHIVW, and RYRLKHLVW, of an A24-restricted Gag **CTL** epitope KYKLKHIVW escaped from being killed by the **CTL** lines, despite the fact that they were recognized when the synthetic peptides corresponding to these variant sequences were exogenously loaded onto the target cells. Thus, their **escape** is likely due to the changes that occur during the processing and presentation of epitopes in the infected cells. Mutations responsible for this mode of **escape** were located within the epitope regions rather than the flanking regions, and such mutations did not influence the virus replication. The results suggest that the impaired antigen processing and presentation often occur in **HIV**-1 field isolates and thus are one of the major mechanisms that enable **HIV**-1 to **escape** from **CTL** recognition. We emphasize the importance of testing **HIV**-1 variants in an endogenous expression system.

L33 ANSWER 6 OF 78 MEDLINE on STN
2003610836. PubMed ID: 14694094. Persistent recognition of autologous virus by high-avidity **CD8** T cells in chronic, progressive **human immunodeficiency virus** type 1 infection. Draenert R; Verrill C L; Tang Y; Allen T M; Wurcel A G; Boczanowski M; Lechner A; Kim A Y; Suscovich T; Brown N V; Addo M M; Walker B D. (Howard Hughes Medical Institute, Partners AIDS Research Center, Massachusetts General Hospital and Harvard Medical School Division of AIDS, Boston, Massachusetts 02129, USA.) Journal of virology, (2004 Jan) 78 (2) 630-41. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB **CD8** T-cell responses are thought to be crucial for control of viremia in **human immunodeficiency virus** (**HIV**) infection but ultimately fail to control viremia in most infected persons. Studies in acute infection have demonstrated strong **CD8**-mediated selection pressure and evolution of mutations conferring **escape** from recognition, but the ability of

CD8 T cell responses that persist in late stage infection to recognize viruses present in vivo has not been determined. Therefore, we studied 24 subjects with advanced **HIV** disease (median viral load = 142,000 copies/ml; median CD4 count = 71/ micro l) and determined **HIV**-1-specific **CD8** T-cell responses to all expressed viral proteins using overlapping peptides by gamma interferon Elispot assay. Chronic-stage virus was sequenced to evaluate autologous sequences within Gag epitopes, and functional avidity of detected responses was determined. In these subjects, the median number of epitopic regions targeted was 13 (range, 2 to 39) and the median cumulative magnitude of **CD8** T-cell responses was 5,760 spot-forming cells/10(6) peripheral blood mononuclear cells (range, 185 to 24,700). On average six (range, one to 8) proteins were targeted. For 89% of evaluated **CD8** T-cell responses, the autologous viral sequence was predicted to be well recognized by these responses and the majority of analyzed optimal epitopes were recognized with medium to high functional avidity by the contemporary **CD8** T cells. Withdrawal of antigen by highly active antiretroviral **therapy** led to a significant decline both in breadth (P = 0.032) and magnitude (P = 0.0098) of these **CD8** T-cell responses, providing further evidence that these responses had been driven by recognition of autologous virus. These results indicate that strong, broadly directed, and high-avidity gamma-interferon-positive **CD8** T-cells directed at autologous virus persist in late disease stages, and the absence of mutations within viral epitopes indicates a lack of strong selection pressure mediated by these responses. These data imply functional impairment of **CD8** T-cell responses in late-stage infection that may not be reflected by gamma interferon-based screening techniques.

L33 ANSWER 7 OF 78 MEDLINE on STN
2003492512. PubMed ID: 14530319. Broadly increased sensitivity to **cytotoxic T lymphocytes** resulting from Nef epitope **escape** mutations. Ali Ayub; Pillai Satish; Ng Hwee; Lubong Rachel; Richman Douglas D; Jamieson Beth D; Ding Yan; McElrath M Juliana; Guatelli John C; Yang Otto O. (Department of Medicine and AIDS Institute, Center for Health Sciences, University of California, Los Angeles, CA 90095, USA.) Journal of immunology (Baltimore, Md. : 1950), (2003 Oct 15) 171 (8) 3999-4005. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB Nef is an **HIV**-1 protein that is absent in most retroviruses, yet its reading frame is highly maintained despite frequent targeting by **CD8**(+) **CTL** in vivo. Because Nef is not necessarily required for viral replication, this consistent maintenance suggests that Nef plays an important role(s) and substantial fitness constraints **prevent** its loss in vivo. The ability of Nef to down-regulate cell surface MHC class I (MHC-I) molecules and render infected cells resistant to **CTL** in general is likely to be an important contributing function. We demonstrate that mutational **escape** of **HIV**-1 from Nef-specific **CTL** in vitro leads to progeny virions that are increased in their susceptibility to **CTL** of specificities for proteins other than Nef. The **escape** mutants contain multiple nef mutations that impair the ability of the virus to down-regulate MHC-I through disruption of its reading frame as well as epitope point mutations. Given the rarity of nef frameshifts in vivo, these data support the concept that the ability to down-regulate MHC-I could be a key constraint for preservation of Nef in vivo.

L33 ANSWER 8 OF 78 MEDLINE on STN
2003463415. PubMed ID: 14526211. AIDS **vaccines** that allow **HIV**-1 to infect and **escape** immunologic control: a mathematic analysis of mass **vaccination**. van Ballegooijen Marijn; Bogaards Johannes A; Weverling Gerrit-Jan; Boerlijst Maarten C; Goudsmit Jaap. (Institute for Biodiversity and Ecosystem Dynamics, Faculty of Science, University of Amsterdam, The Netherlands.) Journal of acquired immune deficiency syndromes (1999), (2003 Oct 1) 34 (2) 214-20. Journal code: 100892005. ISSN: 1525-4135. Pub. country: United States. Language: English.

AB **Cytotoxic T lymphocyte** (**CTL**)-based **HIV vaccine** concepts shown to reduce viremia and postpone disease but not to **prevent** infection in monkeys are currently in human phase 1 trials. To evaluate the potential

efficacy of **vaccines** that cannot **prevent HIV**-1 to infect and **escape** immunologic control, we designed a mathematic model that correlates the level of viremia to both infectiousness and disease progression. We speculate that **vaccinees** will have a virologic set point and disease progression rates comparable to untreated **HIV**-1-infected individuals with the best prognosis. Our model (illustrated with R0 = 3) shows that a sexually active population can ultimately be reduced to 26% of its initial size as a result of AIDS-related mortality in the absence of treatment or **vaccination**. Start of **vaccination** when **HIV**-1 prevalence is still low might postpone the peak incidence of infection and the dramatic decline in population size by up to 22 years. In conclusion, **CTL**-based **vaccines** that do not **prevent HIV**-1 infection but do postpone the time to onset of AIDS have considerable potential to curb the spread of **HIV**-1 and to postpone high AIDS-related mortality on a population level. The number of long-term survivors is substantially increased only when **vaccination** is initiated early in an AIDS epidemic, however.

L33 ANSWER 9 OF 78 MEDLINE on STN
2003441007. PubMed ID: 14500685. Evolution of **CD8**+ T cell immunity and viral **escape** following acute **HIV**-1 infection. Cao Jianhong; McNevin John; Malhotra Uma; McElrath M Juliana. (Program in Infectious Diseases, Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA 98109, USA.) Journal of immunology (Baltimore, Md. : 1950), (2003 Oct 1) 171 (7) 3837-46. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB Induction of **HIV**-1-specific **CD8**(+) T cells during acute infection is associated with a decline in viremia. The role **CD8**(+) effectors play in subsequently establishing viral set point remains unclear. To address this, we focused on two acutely infected patients with the same initial Tat-specific **CD8**(+) response, analyzing their **CD8**(+) T cell responses longitudinally in conjunction with viral load and sequence evolution. In one patient initiating treatment during acute infection, the frequencies of Tat-specific **CD8**(+) T cells gradually diminished but persisted, and the Tat epitope sequence was unaltered. By contrast, in the second patient who declined treatment, the Tat-specific **CD8**(+) T cells disappeared below detection, in conjunction with Gag-specific CD4(+) T cell loss, as plasma viremia reached a set point. This coincided with the emergence of an **escape** variant within the Tat epitope and an additional Vpr epitope. New **CD8**(+) T cell responses emerged but with no further associated decline in viremia. These findings indicate that, in the absence of treatment, the initial **CD8**(+) T cell responses have the greatest impact on reducing viremia, and that later, continuously evolving responses are less efficient in further reducing viral load. The results also suggest that T cell help may contribute to the antiviral efficiency of the acute **CD8**(+) T cell response.

L33 ANSWER 10 OF 78 MEDLINE on STN
2003358818. PubMed ID: 12890631. Prior DNA immunization enhances immune response to dominant and subdominant viral epitopes induced by a fowlpox-based SIVmac **vaccine** in long-term slow-progressor macaques infected with SIVmac251. Radaelli Antonia; Nacsa Janos; Tsai Wen Po; Edghill-Smith Yvette; Zanotto Carlo; Elli Veronica; Venzon David; Tryniszewska Elzbieta; Markham Phil; Mazzara Gail P; Panicali Dennis; De Giuli Morghen Carlo; Franchini Genoveffa. (National Cancer Institute, Basic Research Laboratory, 41/D804, Bethesda, MD 20892-5055, USA.) Virology, (2003 Jul 20) 312 (1) 181-95. Journal code: 0110674. ISSN: 0042-6822. Pub. country: United States. Language: English.

AB A **therapeutic vaccine** for individuals infected with **HIV**-1 and treated with antiretroviral **therapy** (ART) should be able to replenish virus-specific CD4+ T-cells and broaden the virus-specific **CD8**+ T-cell response in order to maintain **CD8**+ T-cell function and minimize viral immune **escape** after ART cessation. Because a combination of DNA and recombinant poxvirus **vaccine** modalities induces high levels of virus-specific CD4+ T-cell response and broadens the cytolytic activity in naive macaques, we investigated whether the same results could be obtained

in SIVmac251 infected macaques. The macaques studied here were long term nonprogressors that naturally contained viremia but were nevertheless treated with a combination of antiviral drugs to assess more carefully the effect of **vaccination** in the context of ART. The combination of a DNA expressing the gag and pol genes (DNA-SIV-gp) of SIVmac239 followed by a recombinant fowlpox expressing the same SIVmac genes (FP-SIV-gp) was significantly more immunogenic than two immunizations of FP-SIV-gp in SIVmac251-infected macaques treated with ART. The DNA/FP combination significantly expanded and broadened Gag-specific T-cell responses measured by tetramer staining, ELISPOT, and intracellular cytokine staining and measurement of ex vivo cytolytic function. Importantly, the combination of these **vaccine** modalities also induced a sizeable expansion in most macaques of Gag-specific **CD8**-(CD4+) T-cells able to produce TNF-alpha. Hopefully, this modality of **vaccine** combination may be useful in the clinical management of **HIV**-1-infected individuals.

L33 ANSWER 11 OF 78 MEDLINE on STN
2003338995. PubMed ID: 12871196. Bioorganic approaches towards **HIV** **vaccine** design. Wang Lai-Xi. (Institute of Human Virology, University of Maryland Biotechnology Institute, University of Maryland, 725 W. Lombard Street, Baltimore, MD 21201, USA.. wangx@umbi.umd.edu) . Current pharmaceutical design, (2003) 9 (22) 1771-87. Journal code: 9602487. ISSN: 1381-6128. Pub. country: Netherlands. Language: English.

AB The worldwide epidemic of **HIV**/AIDS urges the development of an effective **vaccine**. With the identification of **HIV** as the cause of AIDS about two decades ago, it was once expected that a **preventive vaccine** would follow closely behind. But the early promise of **HIV** envelope gp120 as a **preventive vaccine** was not fulfilled. Broadly neutralizing antibodies and **HIV**-specific **cytotoxic T lymphocytes** (**CTL**) are two immune effectors that an effective **HIV vaccine** may have to elicit. Experiments in animal models have proved that sufficient levels of neutralizing antibodies can clean up the virus and protect the animals from viral challenge. Therefore, the induction of a broadly neutralizing antibody response remains a principal goal in **HIV vaccine** development. To achieve persistent infection, **HIV** has evolved elegant strategies to evade host immune surveillance. These include envelope oligomerization, rapid mutation, heavy glycosylation, and conformational changes. Each level of the **HIV's** defenses provides an additional dimension of complexity that has to be taken into account in order to come up with a **vaccine** conferring strong and long lasting immunity. Important progresses have been made in recent years in understanding the structure of **HIV** envelopes and the molecular mechanism of **HIV evasion** to the immune system. This in turn has greatly facilitated a rational design of immunogens capable of eliciting broadly neutralizing antibodies against **HIV**. The present review provides an overview of the major scientific obstacles we are facing in the development of an effective **HIV** **vaccine**, and discusses recent progresses in the field with a focus on current approaches toward a neutralizing antibody-based **HIV vaccine**. The bioorganic aspects of the approaches are emphasized.

L33 ANSWER 12 OF 78 MEDLINE on STN
2003316848. PubMed ID: 12845772. Generation of multivalent genome-wide T cell responses in HLA-A*0201 transgenic mice by an **HIV**-1 expression library immunization (ELI) **vaccine**. Singh Rana A; Barry Michael A. (Rice University, USA.) Research initiative, treatment action : RITA, (2003 Spring) 8 (2) 17-9. Journal code: 100891089. ISSN: 1520-8745. Pub. country: United States. Language: English.

AB **HIV**-1 is a fundamentally difficult target for **vaccines** because of its high mutation rate and its repertoire of immune **evasion** strategies. To address these difficulties, a multivalent genetic **vaccine** or "live genetic **vaccine**" was recently developed against **HIV**-1 using the expression library immunization (ELI) approach. In this **HIV**-1 **vaccine**, all open reading frames of HTLV-IIIb are expressed as protein fragments to retain all viral T cell epitopes, but destroy protein toxicity, inactivate immune **escape** functions, and reveal subdominant epitopes. In addition, each antigen fragment is fused to the ubiquitin

protein to increase antigen expression and target these antigens to the proteasome to enhance **cytotoxic T lymphocyte** (**CTL**) responses. This multivalent **vaccine** also has the advantage of being incapable of generating infectious **HIV**-1 virus because of the segregation of the **HIV** genome into 32 separate plasmids. In this work, we demonstrate the ability of this genetic **vaccine** to provoke robust HLA-A*0201-restricted T cell responses in MHC class I humanized mice against gag, pol, env, and nef after a single round of immunization. In addition, this HTLV-IIIb-derived **vaccine** demonstrated cross-clade, envelope-specific, HLA-restricted **CD8** responses against clades A, D, and E. HLA-restricted **CD8** responses were generated against all 32 open reading frames encoded by the multi-plasmid genetic **vaccine** demonstrating that a broad repertoire of human relevant **CD8** responses are provoked by this **vaccine**. This work supports this approach to generate multivalent T cell responses to control the highly mutable and immuno-evasive **HIV**-1 virus.

L33 ANSWER 13 OF 78 MEDLINE on STN
2003278167. PubMed ID: 12805435. Viral **escape** from dominant simian immunodeficiency virus epitope-specific **cytotoxic T lymphocytes** in DNA-**vaccinated** rhesus monkeys. Barouch Dan H; Kunstman Jennifer; Glowczwskie Jennifer; Kunstman Kevin J; Egan Michael A; Peyerl Fred W; Santra Sampa; Kuroda Marcelo J; Schmitz Jorn E; Beaudry Kristin; Krivulka Georgia R; Lifton Michelle A; Gorgone Darci A; Wolinsky Steven M; Letvin Norman L. (Division of Viral Pathogenesis, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts 02215, USA.. dbarouch@bidmc.harvard.edu) . Journal of virology, (2003 Jul) 77 (13) 7367-75. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Virus-specific **cytotoxic T lymphocytes** (**CTL**) are critical for control of **human immunodeficiency virus** type 1 replication. However, viral **escape** from **CTL** recognition can undermine this immune control. Here we demonstrate the high frequency and pattern of viral **escape** from dominant epitope-specific **CTL** in SIV gag DNA-**vaccinated** rhesus monkeys following a heterologous simian immunodeficiency virus (SIV) challenge. DNA-**vaccinated** monkeys exhibited initial effective control of the SIV challenge, but this early control was lost by serial breakthroughs of viral replication over a 3-year follow-up period. Increases in plasma viral RNA correlated temporally with declines of dominant SIV epitope-specific **CD8**(+) T-lymphocyte responses and the emergence of viral mutations that escaped recognition by dominant epitope-specific **CTL**. Viral **escape** from **CTL** occurred in a total of seven of nine **vaccinated** and control monkeys, including three animals that initially controlled viral replication to undetectable levels of plasma viral RNA. These data suggest that **CTL** exert selective pressure on viral replication and that viral **escape** from **CTL** may be a limitation of **CTL**-based AIDS **vaccine** strategies.

L33 ANSWER 14 OF 78 MEDLINE on STN
2003258247. PubMed ID: 12767994. Dual pressure from antiretroviral **therapy** and cell-mediated immune response on the **human immunodeficiency virus** type 1 protease gene. Karlsson Annika C; Deeks Steven G; Barbour Jason D; Heiken Brandon D; Younger Sophie R; Hoh Rebecca; Lane Meghan; Sallberg Matti; Ortiz Gabriel M; Demarest James F; Liegler Teri; Grant Robert M; Martin Jeffrey N; Nixon Douglas F. (Gladstone Institute of Virology and Immunology, University of California, San Francisco, California 94141, USA.. akarlsson@gladstone.ucsf.edu) . Journal of virology, (2003 Jun) 77 (12) 6743-52. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB **Human immunodeficiency virus** (**HIV**)-specific **CD8**(+) T-lymphocyte pressure can lead to the development of viral **escape** mutants, with consequent loss of immune control. Antiretroviral drugs also exert selection pressures on **HIV**, leading to the emergence of drug resistance mutations and increased levels of viral replication. We have determined a minimal epitope of **HIV** protease, amino acids 76 to 84, towards which a **CD8**(+) T-lymphocyte response is directed. This epitope, which is HLA-A2

restricted, includes two amino acids that commonly mutate (V82A and I84V) in the face of protease inhibitor **therapy**. Among 29 **HIV**-infected patients who were treated with protease inhibitors and who had developed resistance to these drugs, we show that the wild-type PR82V(76-84) epitope is commonly recognized by **cytotoxic T lymphocytes** (**CTL**) in HLA-A2-positive patients and that the **CTL** directed to this epitope are of high avidity. In contrast, the mutant PR82A(76-84) epitope is generally not recognized by wild-type-specific **CTL**, or when recognized it is of low to moderate avidity, suggesting that the protease inhibitor-selected V82A mutation acts both as a **CTL** and protease inhibitor **escape** mutant. Paradoxically, the absence of a mutation at position 82 was associated with the presence of a high-avidity **CD8**(+) T-cell response to the wild-type virus sequence. Our results indicate that both **HIV** type 1-specific **CD8**(+) T cells and antiretroviral drugs provide complex pressures on the same amino acid sequence of the **HIV** protease gene and, thus, can influence viral sequence evolution.

L33 ANSWER 15 OF 78 MEDLINE on STN
2003132433. PubMed ID: 12646660. Viremia control despite **escape** from a rapid and potent autologous neutralizing antibody response after **therapy** cessation in an **HIV**-1-infected individual. Montefiori David C; Altfeld Marcus; Lee Paul K; Bilska Miroslawa; Zhou Jintao; Johnston Mary N; Gao Feng; Walker Bruce D; Rosenberg Eric S. (Department of Surgery, Duke University Medical Center, Durham, NC 27710, USA.. monte@acpub.duke.edu) . Journal of immunology (Baltimore, Md. : 1950), (2003 Apr 1) 170 (7) 3906-14. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB The neutralizing Ab response after primary **HIV**-1 infection is delayed relative to the virus-specific **CD8**(+) T cell response and the initial decline in plasma viremia. Because nearly all **HIV**-1 infections result in AIDS, it would be instructive to study cases where neutralizing Ab production commenced sooner. This was done in subject AC10, an individual treated during early infection and in whom a rapid autologous neutralizing Ab response was detected after **therapy** cessation as rebound viremia declined and remained below 1000 RNA copies/ml of blood for over 2.5 years. This subject's Abs were capable of reducing the infectivity of his rebound virus by >4 logs in vitro at a time when rebound viremia was down-regulated and virus-specific **CD8**(+) T cells were minimal, suggesting that neutralizing Abs played an important role in the early control of viremia. The rebound virus did not exhibit an unusual phenotype that might explain its high sensitivity to neutralization by autologous sera. Neutralization **escape** occurred within 75 days and was proceeded by neutralizing Ab production to the **escape** variant and subsequent **escape**. Notably, **escape** was not associated with a significant rise in plasma viremia, perhaps due to increasing **CD8**(+) T cell responses. Sequence analysis of gp160 revealed a growing number of mutations over time, suggesting ongoing viral evolution in the face of potent antiviral immune responses. We postulate that an early effective neutralizing Ab response can provide long-term clinical benefits despite neutralization **escape**.

L33 ANSWER 16 OF 78 MEDLINE on STN
2003128482. PubMed ID: 12642109. Chimeric immune receptor T cells bypass class I requirements and recognize multiple cell types relevant in **HIV**-1 infection. Severino Michael E; Sarkis Phuong Thi Nguyen; Walker Bruce D; Yang Otto O. (AIDS Research Center and Infectious Disease Unit, Massachusetts General Hospital, Charlestown, MA 02129, USA.) Virology, (2003 Feb 15) 306 (2) 371-5. Journal code: 0110674. ISSN: 0042-6822. Pub. country: United States. Language: English.

AB Transduction of T cells with a chimeric immune T cell receptor (CIR) has been proposed as a strategy to generate cellular immunity against viral pathogens such as **HIV**-1. In the case of the CD4-CD3-zeta chain (CD4-zeta) CIR, specificity for **HIV**-1 is conferred by binding of the CD4 moiety to gp120 on the surface of infected cells. However, it is unclear whether CD4-zeta-T cells may differ from naturally derived **CD8**(+) **cytotoxic T cells** (**CTL**) in their susceptibility to viral **escape**

mechanisms of ability to recognize different cell types that support viral replication. We demonstrate that CIR-T cells can mediate antiviral activity against **HIV**-1 in cells that are resistant to class I-restricted **CTL**-mediated activity. Furthermore, CIR-T cells can suppress virus in multiple cell types, including monocytes, dendritic cells, and lymphocyte-dendritic cell clusters. These results provide evidence that T cells can be redirected against novel targets, and that independence from the class I pathway may have distinct advantages.

L33 ANSWER 17 OF 78 MEDLINE on STN
2002742849. PubMed ID: 12504554. Emergence of **cytotoxic T lymphocyte escape** mutants following antiretroviral treatment suspension in rhesus macaques infected with SIVmac251. Nacsa Janos; Stanton Jennifer; Kunstman Kevin J; Tsai Wen Po; Watkins David I; Wolinsky Steven M; Franchini Genoveffa. (National Cancer Institute, Basic Research Laboratory, 41/D804, Bethesda, Maryland 20892, USA.) Virology, (2003 Jan 5) 305 (1) 210-8. Journal code: 0110674. ISSN: 0042-6822. Pub. country: United States. Language: English.

AB Structured treatment interruption (STI) of antiretroviral drugs has been proposed as an alternative approach for managing patients infected with **HIV**-1. While STI is thought to spare drug-related side effects and enhance the **HIV**-1-specific immune response, the long-lasting clinical benefit of this approach remains uncertain, particularly in patients with long-standing **HIV**-1 infection. Here, we investigated the basis of unabated virological replication following different STI regimens in rhesus macaques that expressed the MHC class I Mamu-A*01 molecule treated during acute and long-standing infection with SIVmac251. An amino acid change at the anchor residue within the immunodominant Mamu-A*01-restricted Gag(181-189) CM9 epitope (T --> A) in one of six macaques with acute SIVmac251 infection and in three of four macaques with long-standing SIVmac251 infection (T --> A; T --> S; S --> C) was found in the majority of plasma virus. These amino acid changes have been shown to severely decrease binding of the corresponding peptides to the Mamu-A*01 molecule and, in the case of the T --> A change, **escape** from **CTL**. In one macaque with long-standing SIVmac251 infection, a mutation emerged that conferred resistance to one of the antiretroviral drugs (PMPA) as well. These results provide insights into the mechanism underlying the limited capacity of repeated interruption of antiretroviral **therapy** as an approach to restrain viral replication. In addition, these data also suggest that interruption of **therapy** may be less effective in chronic infection because of preexisting immune **escape** and that immune **escape** is a risk of interruption of **therapy**.

L33 ANSWER 18 OF 78 MEDLINE on STN
2002734168. PubMed ID: 12496971. T cells versus **HIV**-1: fighting exhaustion as well as **escape**. Robinson Harriet L. Nature immunology, (2003 Jan) 4 (1) 12-3. Journal code: 100941354. ISSN: 1529-2908. Pub. country: United States. Language: English.

L33 ANSWER 19 OF 78 MEDLINE on STN
2002716411. PubMed ID: 12477431. Viral evolution and challenges in the development of **HIV vaccines**. Barouch Dan H; Letvin Norman L. (Beth Israel Deaconess Medical Center, 330 Brookline Avenue, Research East Room 113, Boston, MA 02215, USA.. dan_barouch@hotmail.com) . Vaccine, (2002 Dec 19) 20 Suppl 4 A66-8. Ref: 15. Journal code: 8406899. ISSN: 0264-410X. Pub. country: Netherlands. Language: English.

AB Potent virus-specific **cytotoxic T lymphocyte** (**CTL**) responses elicited by candidate AIDS **vaccines** have been shown to provide short-term control of viral replication following pathogenic viral challenges in rhesus monkeys. We have recently shown that **vaccines** that control rather than **prevent** immunodeficiency virus infections are still subject to immune **escape**. In particular, viral mutations can develop that result in viral **escape** from recognition by immunodominant **CTL**, loss of immune control of viral replication, and clinical disease progression. These data suggest that viral **escape** from **CTL** may prove to be a significant limitation of the current generation of **CTL**-based

AIDS vaccines.

L33 ANSWER 20 OF 78 MEDLINE on STN
2002637569. PubMed ID: 12396608. **Cytotoxic T-lymphocyte escape** monitoring in simian immunodeficiency virus **vaccine** challenge studies. O'Connor David H; Allen Todd M; Watkins David I. (University of Wisconsin at Madison, Department of Pathology, Madison, Wisconsin 53709, USA.. doconnor@primate.wisc.edu) . DNA and cell biology, (2002 Sep) 21 (9) 659-64. Journal code: 9004522. ISSN: 1044-5498. Pub. country: United States. Language: English.

AB Several **vaccine** studies have ameliorated disease progression in simian-**human immunodeficiency virus** (SHIV) infections. The successes of these **vaccines** have been largely attributed to protective effects of **cytotoxic T-lymphocyte** (**CTL**) responses, although the precise correlates of immune protection remain poorly defined. It is now well established that vigorous **CTL** and antibody responses can rapidly select for viral **escape** variants after **HIV** and SIV infection. Here we suggest that viral variation analyses should be performed on viruses derived from **vaccinated**, SIV-, or SHIV-challenged animals as a routine component of **vaccine** evaluation to determine the contribution of immune responses to the success (or failure) of the **vaccine** regimen. To illustrate the importance of **escape** analysis, we show that rapid emergence of **escape** variants postchallenge contributed to the failure of a DNA prime/MVA boost **vaccine** regimen encoding SIV Tat.

L33 ANSWER 21 OF 78 MEDLINE on STN
2002637567. PubMed ID: 12396606. Immunogenicity of **HIV**-1 IIIB and SHIV 89.6P Tat and Tat toxoids in rhesus macaques: induction of humoral and cellular immune responses. Richardson Max W; Mirchandani Jyotika; Silvera Peter; Regulier Emmanuel G; Capini Christelle; Bojczuk Paul M; Hu Jason; Gracely Edward J; Boyer Jean D; Khalili Kamel; Zagury Jean-Francois; Lewis Mark G; Rappaport Jay. (Center for Neurovirology and Cancer Biology, Temple University, Philadelphia, Pennsylvania 19122, USA.) DNA and cell biology, (2002 Sep) 21 (9) 637-51. Journal code: 9004522. ISSN: 1044-5498. Pub. country: United States. Language: English.

AB This study compared immune responses in rhesus macaques immunized with unmodified **HIV**-1 IIIB Tat, SHIV89.6P Tat, and carboxymethylated IIIB and 89.6P Tat toxoids. Immunization with either IIIB or 89.6P preparation induced high titer and broadly crossreactive serum anti-Tat IgG that recognized **HIV**-1 subtype-E and SIVmac251 Tat. However, the response was delayed, and titers were lower in 89.6P **vaccination** groups. Serum anti-Tat IgG recognized peptides corresponding to the amino-terminus, basic domain, and carboxy-terminal region. Cellular proliferative responses to Tat toxoids corresponding to the immunogen were evident in vitro in both IIIB and 89.6P groups. Crossreactive proliferative responses were observed in IIIB groups in response to stimulation with 89.6P or SIVmac251 Tat toxoids, but were much less prevalent in 89.6P groups. The truncated 86 amino acid IIIB Tat appears to be more immunogenic than the 102 amino acid 89.6P Tat with respect to both humoral and cellular immune responses, and may be a better **vaccine** component. Despite induction of robust humoral and cellular immune responses (including both CD4+ and **CD8**+ T-cell responses) to Tat, all animals were infected upon intravenous challenge with 30 MID(50) of SHIV89.6P and outcome of **vaccine** groups was not different from controls. Sequencing both Tat exons from serum viral RNA revealed no evidence of **escape** mutants. These results suggest that with intravenous SHIV89.6P challenge in rhesus macaques, precipitous CD4+ T-cell decline overwhelms potentially protective immune responses. Alternatively, Tat specific **CD8**+ T-cell responses may not appropriately recognize infected cells in vivo in this model. In view of evidence demonstrating Tat specific CTLs in the SIV model and in humans infected with **HIV**-1, results in this pathogenic SHIV model may not apparently predict the efficacy of this approach in human studies. The potency and cross-reactivity of these immune responses confirm Tat toxoid as an excellent candidate **vaccine** component.

L33 ANSWER 22 OF 78 MEDLINE on STN

2002633205. PubMed ID: 12370500. Antiviral activity of the neutralizing antibodies 2F5 and 2G12 in asymptomatic **HIV**-1-infected humans: a phase I evaluation. Stiegler Gabriela; Armbruster Christine; Vcelar Brigitta; Stoiber Heribert; Kunert Renate; Michael Nelson L; Jagodzinski Linda L; Ammann Christoph; Jager Walter; Jacobson Jeffrey; Vetter Norbert; Katinger Hermann. (Institute of Applied Microbiology, University of Agricultural Sciences, Muthgasse, Vienna, Austria.. G.Stiegler@iam.boku.ac.at) . AIDS (London, England), (2002 Oct 18) 16 (15) 2019-25. Journal code: 8710219. ISSN: 0269-9370. Pub. country: England: United Kingdom. Language: English.

AB BACKGROUND: The human monoclonal antibodies (MAbs) 2F5 and 2G12 were identified to be two of the most potent neutralizing antibodies against **HIV**-1. In a first human study they have been shown to be safe after repeated intravenous infusions to asymptomatic **HIV**-1-infected individuals. However, the antiviral effects of antibody treatment have not been fully analyzed in this first clinical trial. METHODS: The aim of the present study was to gain a preliminary insight into the antiviral effects of 2F5 and 2G12 in humans. For this purpose, plasma samples obtained from the previous phase I study were studied for RNA copy numbers by reverse transcriptase-polymerase chain reaction. As a measure for activation of complement levels of the major complement factor C3 were measured by enzyme-linked immunosorbent assay. Flow cytometry was used to study T-lymphocyte counts and the amount of infected peripheral blood mononuclear cells (PBMC) was determined by co-culture with uninfected donor PBMC. Virus **escape** from antibody neutralization was determined in vitro in a PBMC neutralization assay. RESULTS: Transient reduction in viral loads was observed in five of seven patients. Vigorous complement activation was observed directly after **HIV**-specific antibody infusions. The number of infective peripheral blood mononuclear cells was reduced in some patients whereas CD4+ T-lymphocyte counts and CD4+/**CD8**+ ratios were transiently increased in all patients. Virus **escape** occurred only against 2G12. CONCLUSIONS: Analysis of disease progression markers indicate that antibody **therapy** may have antiviral effects. These findings suggest that neutralizing antibodies should be further evaluated as an alternative **therapeutic** approach in **HIV**-1 disease.

L33 ANSWER 23 OF 78 MEDLINE on STN
2002493067. PubMed ID: 12355422. NK cell activity controls human herpesvirus 8 latent infection and is restored upon highly active antiretroviral **therapy** in AIDS patients with regressing Kaposi's sarcoma. Sirianni Maria Caterina; Vincenzi Laura; Topino Simone; Giovannetti Antonello; Mazzetta Francesca; Libi Fabio; Scaramuzzi Donato; Andreoni Massimo; Pinter Elena; Baccarini Sara; Rezza Giovanni; Monini Paolo; Ensoli Barbara. (Department of Clinical Immunology, University of Rome La Sapienza, Viale dell'Universita 37, I-00185 Rome, Italy.. mariacaterina.sirianni@uniroma1.it) . European journal of immunology, (2002 Oct) 32 (10) 2711-20. Journal code: 1273201. ISSN: 0014-2980. Pub. country: Germany: Germany, Federal Republic of. Language: English.

AB Kaposi's sarcoma (KS) develops upon reactivation of human herpesvirus 8 (HHV8) infection and virus dissemination to blood and tissue cells, including endothelial and KS spindle cells where the virus is mostly present in a latent form. However, this may likely require the presence of compromised host immune responses and/or the **evasion** of infected cells from the host immune response.In this regard, mechanisms of **evasion** of productively infected cells from both **CTL** and NK cell responses, and resistance of latently infected cells from specific **CTL**, have already been shown. Here we show that cells which are latently infected by HHV8 are indeed efficiently lysed by NK cells from individuals with a normal immune response. Notably, NK cell-mediated immunity was found to be significantly reduced in AIDS patients with progressing KS as compared to both **HIV**-negative patients with indolent classic KS or normal blood donors. However, it was restored after treatment with the highly active antiretroviral **therapy** (HAART) in AIDS-KS patients, that showed regression and clearance of HHV8 from PBMC. By contrast, AIDS-KS patients with a more aggressive disease and no clinical response had persistent HHV8 viremia associated with reduced NK cell cytotoxicity.

These results suggest a key role for NK cells in the control of HHV8 latent infection, KS development, and in disease remission upon HAART.

L33 ANSWER 24 OF 78 MEDLINE on STN
2002485968. PubMed ID: 12239290. Magnitude and frequency of **cytotoxic T-lymphocyte** responses: identification of immunodominant regions of **human immunodeficiency virus** type 1 subtype C. Novitsky V; Cao H; Rybak N; Gilbert P; McLane M F; Gaolekwe S; Peter T; Thior I; Ndung'u T; Marlink R; Lee T H; Essex M. (Department of Immunology and Infectious Diseases, Harvard School of Public Health, FXB-402, 651 Huntington Avenue, Boston, MA 02115, USA.) Journal of virology, (2002 Oct) 76 (20) 10155-68. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB A systematic analysis of immune responses on a population level is critical for a **human immunodeficiency virus** type 1 (**HIV**-1) **vaccine** design. Our studies in Botswana on (i) molecular analysis of the **HIV**-1 subtype C (**HIV**-1C) epidemic, (ii) frequencies of major histocompatibility complex class I HLA types, and (iii) **cytotoxic T-lymphocyte** (**CTL**) responses in the course of natural infection allowed us to address **HIV**-1C-specific immune responses on a population level. We analyzed the magnitude and frequency of the gamma interferon ELISPOT-based **CTL** responses and translated them into normalized cumulative **CTL** responses. The introduction of population-based cumulative **CTL** responses reflected both (i) essentials of the predominant virus circulating locally in Botswana and (ii) specificities of the genetic background of the Botswana population, and it allowed the identification of immunodominant regions across the entire **HIV**-1C. The most robust and vigorous immune responses were found within the **HIV**-1C proteins Gag p24, Vpr, Tat, and Nef. In addition, moderately strong responses were scattered across Gag p24, Pol reverse transcriptase and integrase, Vif, Tat, Env gp120 and gp41, and Nef. Assuming that at least some of the immune responses are protective, these identified immunodominant regions could be utilized in designing an **HIV vaccine** candidate for the population of southern Africa. Targeting multiple immunodominant regions should improve the overall **vaccine** immunogenicity in the local population and minimize viral **escape** from immune recognition. Furthermore, the analysis of **HIV**-1C-specific immune responses on a population level represents a comprehensive systematic approach in **HIV vaccine** design and should be considered for other **HIV**-1 subtypes and/or different geographic areas.

L33 ANSWER 25 OF 78 MEDLINE on STN
2002406592. PubMed ID: 12160861. **HIV**: current opinion in escapology. Klenerman Paul; Wu Ying; Phillips Rodney. (Peter Medawar Building for Pathogen Research, University of Oxford, South Parks Road, OX1 3SY, Oxford, UK.. klener@molbiol.ox.ac.uk) . Current opinion in microbiology, (2002 Aug) 5 (4) 408-13. Ref: 49. Journal code: 9815056. ISSN: 1369-5274. Pub. country: England: United Kingdom. Language: English.

AB Much recent work strongly supports the hypothesis that **CD8**(+) T lymphocytes (CTLs) exert important immune control over **HIV** and so are a major selective force in its evolution. We analyse this host-pathogen interplay and focus on new data that describe the overall 'effectiveness' of **CTL** responses (strength, spread, specificity and 'stamina') and the mechanisms by which **HIV** may evade this suppressive activity. CTLs directed against **HIV** recognise very large numbers of distinct epitopes across the genome, are largely functional, turn over rapidly, and possess a phenotype that is distinct from **CD8**(+) lymphocytes specific for other viruses. Mutation of **HIV** epitopes that alters or abolishes **CTL** recognition altogether appears to be the most important immune **escape** mechanism, as the variation that **HIV** generates defies the limits of the T cell repertoire. However, this immune **evasion** is still only well-studied in a few patients. The rules that govern immune **escape**, and the ultimate limits of **CTL** capacity to deal with the variant epitopes that currently circulate, are not understood. This information will determine the feasibility of current **vaccine** approaches that, so far, make no provision for the enormous antigenic plasticity of **HIV**.

L33 ANSWER 26 OF 78 MEDLINE on STN
2002376943. PubMed ID: 12097549. **Human immunodeficiency virus**-specific **CD8**(+) T cells in human breast milk. Sabbaj Steffanie; Edwards Bradley H; Ghosh Mrinal K; Semrau Katherine; Cheelo Sanford; Thea Donald M; Kuhn Louise; Ritter G Douglas; Mulligan Mark J; Goepfert Paul A; Aldrovandi Grace M. (Departments of Medicine, University of Alabama at Birmingham, 35294-2170, USA.) Journal of virology, (2002 Aug) 76 (15) 7365-73. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Breast-feeding infants of **human immunodeficiency virus** (**HIV**)-infected women ingest large amounts of **HIV**, but most **escape** infection. While the factors affecting transmission risk are poorly understood, **HIV**-specific **cytotoxic T-lymphocyte** (**CTL**) responses play a critical role in controlling **HIV** levels in blood. We therefore investigated the ability of breast milk cells (BMC) from **HIV**-infected women from the United States and Zambia to respond to **HIV**-1 peptides in a gamma interferon enzyme-linked immunospot assay. All (n = 11) **HIV**-infected women had responses to pools of Gag peptide (range, 105 to 1,400 spot-forming cells/million; mean = 718), 8 of 11 reacted to Pol, 7 reacted to Nef, and 2 of 5 reacted to Env. Conversely, of four **HIV**-negative women, none responded to any of the tested **HIV** peptide pools. Depletion and tetramer staining studies demonstrated that **CD8**(+) T cells mediated these responses, and a chromium-release assay showed that these BMC were capable of lysing target cells in an **HIV**-specific manner. These data demonstrate the presence of **HIV**-specific major histocompatibility complex class I-restricted **CD8**(+) CTLs in breast milk. Their presence suggests a role in limiting transmission and provides a rationale for **vaccine** strategies to enhance these responses.

L33 ANSWER 27 OF 78 MEDLINE on STN
2002277897. PubMed ID: 12018459. Neutralizing antibodies mechanism of neutralization and protective activity against **HIV**-1. Xiao Yi; Dong Xiaonan; Chen Ying-Hua. (Research Centre for Medical Science, Department of Biology, Tsinghua University, Beijing, P.R. China.) Immunologic research, (2002) 25 (3) 193-200. Ref: 48. Journal code: 8611087. ISSN: 0257-277X. Pub. country: United States. Language: English.

AB The role of the humoral immune response in **prevention** against **HIV**-1 infection is still incompletely understood. However, neutralizing antibodies to certain epitopes on **HIV**-1 envelope glycoproteins inhibit **HIV**-1 infection in vitro and in vivo. Passive administration of these antibodies by themselves or in combination completely protected hu-PBL-SCID mice or macaques from intravenous, vaginal, as well as maternal-fetal mucosal transmission. All these studies provide direct experimental evidence that neutralizing antibodies are potent enough to **prevent HIV** infection, and strongly suggest that neutralizing-antibody-based **vaccines** could provide effective protection against **HIV**-1, despite the potent action of CTLs. Some neutralizing epitopes have been defined in vitro and in vivo. Unfortunately, none of the neutralizing-antibody-based candidate **vaccines** has been demonstrated to induce enough protective activity. Weak antigenicity and immunogenicity of neutralizing epitopes on native or recombinant proteins and other factors made it difficult to induce neutralizing-epitope-specific antibody responses in vivo enough to **prevent** against primary isolates. Recent studies indicated that **HIV**-1 variations resulted in **escape** from neutralization or the **CTL** responses, which may be the principal challenge for **HIV**-1 **prevention**. Epitope **vaccine** as a new strategy activating both arms of the immune system, namely, using the "principal neutralizing epitopes" and the **CTL** epitopes in combination, should provide new hope for developing an effective **vaccine** to halt the **HIV**-1 epidemic.

L33 ANSWER 28 OF 78 MEDLINE on STN
2002070858. PubMed ID: 11797012. Eventual AIDS **vaccine** failure in a rhesus monkey by viral **escape** from **cytotoxic T lymphocytes**. Barouch Dan H; Kunstman Jennifer; Kuroda Marcelo J; Schmitz Jorn E; Santra

Sampa, Peyerl Fred W; Krivulka Georgia R; Beaudry Kristin; Lifton Michelle A; Gorgone Darci A; Montefiori David C; Lewis Mark G; Wolinsky Steven M; Letvin Norman L. (Department of Medicine, Harvard Medical School, Beth Israel Deaconess Medical Center, Research East Room 113, 330 Brookline Avenue, Boston, Massachusetts 02215, USA.. dan_barouch@hotmail.com) . Nature, (2002 Jan 17) 415 (6869) 335-9. Journal code: 0410462. ISSN: 0028-0836. Pub. country: England: United Kingdom. Language: English.

AB Potent virus-specific **cytotoxic T lymphocyte** (**CTL**) responses elicited by candidate AIDS **vaccines** have recently been shown to control viral replication and **prevent** clinical disease progression after pathogenic viral challenges in rhesus monkeys. Here we show that viral **escape** from **CTL** recognition can result in the eventual failure of this partial immune protection. Viral mutations that **escape** from **CTL** recognition have been previously described in humans infected with **human immunodeficiency virus** (**HIV**) and monkeys infected with simian immunodeficiency virus (SIV). In a cohort of rhesus monkeys that were **vaccinated** and subsequently infected with a pathogenic hybrid simian-**human immunodeficiency virus** (SHIV), the frequency of viral sequence mutations within **CTL** epitopes correlated with the level of viral replication. A single nucleotide mutation within an immunodominant Gag **CTL** epitope in an animal with undetectable plasma viral RNA resulted in viral **escape** from CTLs, a burst of viral replication, clinical disease progression, and death from AIDS-related complications. These data indicate that viral **escape** from **CTL** recognition may be a major limitation of the **CTL**-based AIDS **vaccines** that are likely to be administered to large human populations over the next several years.

L33 ANSWER 29 OF 78 MEDLINE on STN

2002056314. PubMed ID: 11782252. Understanding **cytotoxic T-lymphocyte escape** during simian immunodeficiency virus infection. O'Connor D; Friedrich T; Hughes A; Allen T M; Watkins D. Immunological reviews, (2001 Oct) 183 115-26. Ref: 101. Journal code: 7702118. ISSN: 0105-2896. Pub. country: Denmark. Language: English.

AB Infection of rhesus macaques with simian immunodeficiency virus (SIV) is an excellent model system for studying viral adaptation to immune responses. In this review, we discuss how the SIV-infected macaque has provided unequivocal evidence for **cytotoxic T-lymphocyte** (**CTL**) selection of viral **escape** variants. This improved understanding of **CTL escape** may influence **human immunodeficiency virus** (**HIV**) **vaccine** design as well as our understanding of **HIV** pathogenesis.

L33 ANSWER 30 OF 78 MEDLINE on STN

2001548922. PubMed ID: 11595292. **Vaccination** with **CTL** epitopes that **escape**: an alternative approach to **HIV vaccine** development?. O'Connor D; Allen T; Watkins D I. (Department of Pathology, Wisconsin Regional Primate Centre, University of Wisconsin, 1220 Capitol Court, Madison, WI 53715-1299, USA.) Immunology letters, (2001 Nov 1) 79 (1-2) 77-84. Journal code: 7910006. ISSN: 0165-2478. Pub. country: Netherlands. Language: English.

AB This article describes a novel approach to **HIV vaccine** design that is, as yet, unproven and still in preliminary development. In rhesus macaques infected with simian immunodeficiency virus (SIV), we have identified particular cellular immune responses that select for viral variants during primary infection. We speculate that the detection of viral variants with altered amino acids in **CTL** epitopes implies the successful clearance of cells harboring wild-type virus. Here, we present our rationale suggesting why such potent early **CTL** responses that exert an antiviral effect may be particularly attractive targets for induction by candidate **vaccines**. Conventional wisdom suggests that regions of the virus that are structurally and functionally important will generally be well-conserved both among clades and within an infected host. Amino acid replacements within these well-conserved regions should be difficult for the virus to accommodate. Therefore, these regions are traditionally considered ideal targets for **vaccine** induced immune responses because they are refractory to **CTL escape** mutations. Many examples of these regions have been identified in both **HIV**-1 and SIV(mac) (J. Immunol.

102 (1999) 3727; J. Virol. 67 (1993) 438) and have been included in candidate **vaccine** formulations. Human clinical trials testing these **vaccines** are currently underway. Our proposed method of **vaccination** with **CTL** epitopes that **escape** explores an alternative hypothesis. Rather than engendering responses to regions of the virus that do not **escape**, we reason that **vaccination** needs to accelerate the development of the initial immune responses that effectively select for amino acid variants during acute infection. By examining **CTL escape** during the acute phase, we will identify **CTL** responses that the virus cannot tolerate and incorporate these responses into **vaccines**.

L33 ANSWER 31 OF 78 MEDLINE on STN
2001534011. PubMed ID: 11580226. Dendritic cell **vaccination** induces cross-reactive **cytotoxic T lymphocytes** specific for wild-type and natural variant **human immunodeficiency virus** type 1 epitopes in HLA-A*0201/Kb transgenic mice. Abdel-Motal U M; Friedline R; Poligone B; Pogue-Caley R R; Frelinger J A; Tisch R. (Department of Microbiology and Immunology, University of North Carolina, Chapel Hill, North Carolina 27599, USA.) Clinical immunology (Orlando, Fla.), (2001 Oct) 101 (1) 51-8. Journal code: 100883537. ISSN: 1521-6616. Pub. country: United States. Language: English.

AB Dendritic cells (DC) are highly efficient at inducing primary T cell responses. Consequently, DC are being investigated for their potential to **prevent** and/or treat **human immunodeficiency virus** type 1 (**HIV**-1) infection. In the current study, we examined the capacity of DC to elicit **CD8+ cytotoxic T lymphocyte** (**CTL**) reactivity against an HLA-A*0201-restricted **HIV**-1 reverse transcriptase (pol) epitope (residues 476-484) and two naturally occurring variants. Previous work demonstrated that the wild-type pol epitope is recognized by CTLs from **HIV**-1-infected individuals, whereas the variant pol epitopes are not, despite binding to HLA-A*0201. In agreement with these observations, parenteral administration of wild-type pol peptide induced HLA-A*0201-restricted **CTL** activity in A2Kb transgenic mice. In contrast, similar treatment with the two variant pol peptides failed to stimulate **CTL** reactivity, and this lack of immunogenicity correlated with reduced peptide:HLA-A*0201 complex stability. However, **CTL** responses were induced in A2Kb transgenic mice upon adoptive transfer of syngeneic bone marrow DC pulsed with the variant pol peptides. Furthermore, DC pulsed with the wild-type pol peptide elicited CTLs that cross-reacted with the variant pol epitopes. These results demonstrate that DC effectively expand the T cell repertoire of a given epitope to include cross-reactive T cell clonotypes. Accordingly, DC **vaccination** may aid in immune recognition of **HIV**-1 **escape** variants by broadening the T cell response.

L33 ANSWER 32 OF 78 MEDLINE on STN
2001532248. PubMed ID: 11578695. Deletion of N-terminal myristoylation site of **HIV** Nef abrogates both MHC-1 and CD4 down-regulation. Peng B; Robert-Guroff M. (Basic Research Laboratory, National Cancer Institute, National Institutes of Health, 41 Libary Drive, Building 41 Room d804, Bethesda, MD 20892-5055, USA.. guroffm@exchange.nih.gov) . Immunology letters, (2001 Oct 1) 78 (3) 195-200. Journal code: 7910006. ISSN: 0165-2478. Pub. country: Netherlands. Language: English.

AB **HIV**-1 Nef is a desirable **vaccine** component because it is expressed early and abundantly during **HIV** infection, and contains many **CTL**, T-helper cell, and B-cell epitopes. Nef, however, down-regulates MHC-1 and CD4 cell surface expression, contributing to viral **escape** from host immunity. To **prevent** Nef from down-regulating both MHC-1 and CD4 while preserving most **CTL** epitopes, a panel of Nef mutants was constructed and assessed. Some mutants, as expected, modulated either MHC-1 or CD4 expression. Others **prevented** down-regulation of both proteins but sacrificed numerous immunogenic epitopes. Deletion of 19 N-terminal amino acids including the myristoylation signal from Nef completely abrogated both MHC-1 and CD4 down-regulation while preserving most **CTL**, T-helper and B-cell epitopes. Our results demonstrate that the myristoylation

signal in the Nef protein is critical for Nef mediated endocytosis of both MHC-1 and CD4. Non-myristoylated Nef containing a full complement of **CTL** epitopes has greater potential as a **vaccine** component than wild-type Nef.

L33 ANSWER 33 OF 78 MEDLINE on STN
2001424537. PubMed ID: 11460164. Evolution and transmission of stable **CTL escape** mutations in **HIV** infection. Goulder P J; Brander C; Tang Y; Tremblay C; Colbert R A; Addo M M; Rosenberg E S; Nguyen T; Allen R; Trocha A; Altfeld M; He S; Bunce M; Funkhouser R; Pelton S I; Burchett S K; McIntosh K; Korber B T; Walker B D. (Partners AIDS Research Center, Massachusetts General Hospital and Division of AIDS, Harvard Medical School, Boston, Massachusetts 02114, USA.. goulder@helix.mg.harvard.edu) . Nature, (2001 Jul 19) 412 (6844) 334-8. Journal code: 0410462. ISSN: 0028-0836. Pub. country: England: United Kingdom. Language: English.

AB Increasing evidence indicates that potent anti-**HIV**-1 activity is mediated by **cytotoxic T lymphocytes** (CTLs); however, the effects of this immune pressure on viral transmission and evolution have not been determined. Here we investigate mother-child transmission in the setting of human leukocyte antigen (HLA)-B27 expression, selected for analysis because it is associated with prolonged immune containment in adult infection. In adults, mutations in a dominant and highly conserved B27-restricted Gag **CTL** epitope lead to loss of recognition and disease progression. In mothers expressing HLA-B27 who transmit **HIV**-1 perinatally, we document transmission of viruses encoding **CTL escape** variants in this dominant Gag epitope that no longer bind to B27. Their infected infants target an otherwise subdominant B27-restricted epitope and fail to contain **HIV** replication. These **CTL escape** variants remain stable without reversion in the absence of the evolutionary pressure that originally selected the mutation. These data suggest that **CTL escape** mutations in epitopes associated with suppression of viraemia will accumulate as the epidemic progresses, and therefore have important implications for **vaccine** design.

L33 ANSWER 34 OF 78 MEDLINE on STN
2001322334. PubMed ID: 11157050. Impairment of CD4(+) T cell responses during chronic virus infection **prevents** neutralizing antibody responses against virus **escape** mutants. Ciurea A; Hunziker L; Klenerman P; Hengartner H; Zinkernagel R M. (Institute for Experimental Immunology, University Hospital, CH-8091 Zurich, Switzerland.. adrian.ciurea@dim.usz.ch) . Journal of experimental medicine, (2001 Feb 5) 193 (3) 297-305. Journal code: 2985109R. ISSN: 0022-1007. Pub. country: United States. Language: English.

AB We have shown previously that neutralizing antibodies (nAbs) are important contributors to the long-term immune control of lymphocytic choriomeningitis virus infection, particularly if **cytotoxic T cell** responses are low or absent. Nevertheless, virus **escape** from the nAb response due to mutations within the surface glycoprotein gene may subsequently allow the virus to persist. Here we show that most of the antibody-**escape** viral mutants retain their immunogenicity. We present evidence that the failure of the infected host to mount effective humoral responses against emerging neutralization-**escape** mutants correlates with the rapid loss of CD4(+) T cell responsiveness during the establishment of viral persistence. Similar mechanisms may contribute to the persistence of some human pathogens such as hepatitis B and C viruses, and **human immunodeficiency virus**.

L33 ANSWER 35 OF 78 MEDLINE on STN
2001278625. PubMed ID: 11362020. Primary **HIV**-1 infection: a review of clinical manifestations, immunologic and virologic changes. Kaufmann G R; Duncombe C; Zaunders J; Cunningham P; Cooper D. (Centre for Immunology, St. Vincent's Hospital, Sydney, Australia.. Kaufmann@arnie.cfi.unsw.edu.au) . AIDS patient care and STDs, (1998 Oct) 12 (10) 759-67. Ref: 63. Journal code: 9607225. ISSN: 1087-2914. Pub. country: United States. Language: English.

AB In the past few years, major advances have been made in the field of

primary **HIV**-1 infection. Several studies have reevaluated the clinical syndrome. The emergence of new molecular laboratory techniques has permitted a detailed analysis of viral dynamics and subsequent immunologic changes. Measurements of subsets of T-lymphocytes have allowed greater insight into the early pathogenesis of **HIV**-1 disease. There is now evidence that **HIV**-1-specific **cytotoxic T-lymphocytes** occur early during primary **HIV**-1 infection and are probably the most important immune defense against **HIV**-1. However, **HIV**-1 immune **escape** mutants have been identified during primary infection, which may be one reason for the failure of the immune system to completely eradicate the virus. Cytokines have been shown to play a role in primary **HIV**-1 infection, and the **therapy** of primary infection has gained more interest due to the introduction of potent triple combinations, including protease inhibitors.

L33 ANSWER 36 OF 78 MEDLINE on STN
2001256876. PubMed ID: 11148221. Cellular immune responses and viral diversity in individuals treated during acute and early **HIV**-1 infection. Altfeld M; Rosenberg E S; Shankarappa R; Mukherjee J S; Hecht F M; Eldridge R L; Addo M M; Poon S H; Phillips M N; Robbins G K; Sax P E; Boswell S; Kahn J O; Brander C; Goulder P J; Levy J A; Mullins J I; Walker B D. (Partners AIDS Research Center and Infectious Disease Unit, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts 02129, USA.) Journal of experimental medicine, (2001 Jan 15) 193 (2) 169-80. Journal code: 2985109R. ISSN: 0022-1007. Pub. country: United States. Language: English.

AB Immune responses induced during the early stages of chronic viral infections are thought to influence disease outcome. Using **HIV** as a model, we examined virus-specific **cytotoxic T lymphocytes** (CTLs), T helper cells, and viral genetic diversity in relation to duration of infection and subsequent response to antiviral **therapy**. Individuals with acute **HIV**-1 infection treated before seroconversion had weaker **CTL** responses directed at fewer epitopes than persons who were treated after seroconversion. However, treatment-induced control of viremia was associated with the development of strong T helper cell responses in both groups. After 1 yr of antiviral treatment initiated in acute or early infection, all epitope-specific **CTL** responses persisted despite undetectable viral loads. The breadth and magnitude of **CTL** responses remained significantly less in treated acute infection than in treated chronic infection, but viral diversity was also significantly less with immediate **therapy**. We conclude that early treatment of acute **HIV** infection leads to a more narrowly directed **CTL** response, stronger T helper cell responses, and a less diverse virus population. Given the need for T helper cells to maintain effective **CTL** responses and the ability of virus diversification to accommodate immune **escape**, we hypothesize that early **therapy** of primary infection may be beneficial despite induction of less robust **CTL** responses. These data also provide rationale for **therapeutic** immunization aimed at broadening **CTL** responses in treated primary **HIV** infection.

L33 ANSWER 37 OF 78 MEDLINE on STN
2001247940. PubMed ID: 11289809. **HIV**-1 Nef blocks transport of MHC class I molecules to the cell surface via a PI 3-kinase-dependent pathway. Swann S A; Williams M; Story C M; Bobbitt K R; Fleis R; Collins K L. (Departments of Medicine and Microbiology and Immunology, The University of Michigan, Ann Arbor, Michigan 48109, USA.) Virology, (2001 Apr 10) 282 (2) 267-77. Journal code: 0110674. ISSN: 0042-6822. Pub. country: United States. Language: English.

AB **HIV** causes a chronic infection by evading immune eradication. A key element of **HIV** immune **escape** is the **HIV**-1 Nef protein. Nef causes a reduction in the level of cell surface major histocompatibility complex class I (MHC-I) protein expression, thus protecting **HIV**-infected cells from anti-**HIV** **cytotoxic T lymphocyte** (**CTL**) recognition and killing. Nef also reduces cell surface levels of the **HIV** receptor, CD4, by accelerating endocytosis. We show here that endocytosis is not required for Nef-mediated downmodulation of MHC-I molecules. The main effect of Nef is to block transport of MHC-I molecules to the cell

surface, leading to accumulation in intracellular organelles.
Furthermore, the effect of Nef on MHC-I molecules (but not on CD4) requires phosphoinositide 3-kinase (PI 3-kinase) activity. We propose that Nef diverts MHC-1 proteins into a PI 3-kinase-dependent transport pathway that **prevents** expression on the cell surface.

L33 ANSWER 38 OF 78 MEDLINE on STN
2001219421. PubMed ID: 11309628. Cellular immune responses to **HIV**.
McMichael A J; Rowland-Jones S L. (MRC Human Immunology Unit, Institute of Molecular Medicine, John Radcliffe Hospital, Oxford OX3 9DS, UK.) Nature, (2001 Apr 19) 410 (6831) 980-7. Ref: 110. Journal code: 0410462. ISSN: 0028-0836. Pub. country: England: United Kingdom. Language: English.

AB The cellular immune response to the **human immunodeficiency virus**, mediated by T lymphocytes, seems strong but fails to control the infection completely. In most virus infections, T cells either eliminate the virus or suppress it indefinitely as a harmless, persisting infection. But the **human immunodeficiency virus** undermines this control by infecting key immune cells, thereby impairing the response of both the infected CD4+ T cells and the uninfected **CD8**+ T cells. The failure of the latter to function efficiently facilitates the **escape** of virus from immune control and the collapse of the whole immune system.

L33 ANSWER 39 OF 78 MEDLINE on STN
2001102747. PubMed ID: 11118377. Temporal loss of Nef-epitope **CTL** recognition following macaque lipopeptide immunization and SIV challenge.
Mortara L; Letourneur F; Villefroy P; Beyer C; Gras-Masse H; Guillet J G; Bourgault-Villada I. (Laboratoire d'Immunologie des Pathologies Infectieuses et Tumorales, Institut Cochin de Genetique Moleculaire (ICGM), INSERM U445, 27 rue du Faubourg Saint-Jacques, Paris, 75014, France.) Virology, (2000 Dec 20) 278 (2) 551-61. Journal code: 0110674. ISSN: 0042-6822. Pub. country: United States. Language: English.

AB To address the subtle interactions between antiviral **cytotoxic T-cell** (**CTL**) immune responses and the evolution of viral quasispecies variants in vivo, we performed a longitudinal study in a simian immunodeficiency virus (SIV)-infected rhesus macaque that had a long experimental SIV infection before developing simian AIDS. Before being infected with SIV, this animal was immunized with a mixture of seven lipopeptides derived from SIV Nef and Gag proteins and showed a bispecific antiviral **CTL** response directed toward Nef 169-178 and 211-225 peptides. After SIV infection, **CTL** activity against the Nef 169-178 epitope was no longer detectable, as assessed from peripheral blood mononuclear cells stimulated by autologous SIV. **CTL** activity against the 211-225 epitope was lost after 3 months, and an additional **CTL** response to the amino acids 112-119 Nef epitope emerged. Analysis of the Nef proviral sequence revealed the presence of immune **escape** variants first in the 211-225 epitope and much later in the 112-119 epitope. In contrast, epitope 169-178 showed only two mutations among all viral sequencing performed. We conclude that in this macaque, bispecific **CTL** exerted a strong selective pressure and **escape** virus mutants finally emerged. We identified **CTL** recognizing a conserved Nef epitope 112-119 (SYKLAIDM), essential for viral replication, which could be associated with a prolonged AIDS-free period. These results stress the importance of the induction of broader multispecific CTLs directed against highly conserved and functional T-cell epitopes by **vaccination**, with the aim of keeping **HIV** infection in check.

L33 ANSWER 40 OF 78 MEDLINE on STN
2001022020. PubMed ID: 10666241. T-cell receptor-mediated anergy of a **human immunodeficiency virus** (**HIV**) gp120-specific CD4(+) **cytotoxic T-cell** clone, induced by a natural **HIV** type 1 variant peptide.
Bouhdoud L; Villain P; Merzouki A; Arella M; Couture C. (Molecular Oncology Group, Lady Davis Institute for Medical Research, Montreal, Quebec, Canada.) Journal of virology, (2000 Mar) 74 (5) 2121-30. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United

States. Language: English.

AB **Human immunodeficiency virus** type 1 (**HIV**-1) infection triggers a **cytotoxic T-lymphocyte** (**CTL**) response mediated by **CD8**(+) and perhaps CD4(+) CTLs. The mechanisms by which **HIV**-1 escapes from this **CTL** response are only beginning to be understood. However, it is already clear that the extreme genetic variability of the virus is a major contributing factor. Because of the well-known ability of altered peptide ligands (APL) to induce a T-cell receptor (TCR)-mediated anergic state in CD4(+) helper T cells, we investigated the effects of **HIV**-1 sequence variations on the proliferation and cytotoxic activation of a human CD4(+) **CTL** clone (Een217) specific for an epitope composed of amino acids 410 to 429 of **HIV**-1 gp120. We report that a natural variant of this epitope induced a functional anergic state rendering the T cells unable to respond to their antigenic ligand and **preventing** the proliferation and cytotoxic activation normally induced by the original antigenic peptide. Furthermore, the stimulation of Een217 cells with this APL generated altered TCR-proximal signaling events that have been associated with the induction of T-cell anergy in CD4(+) T cells. Importantly, the APL-induced anergic state of the Een217 T cells could be **prevented** by the addition of interleukin 2, which restored their ability to respond to their nominal antigen. Our data therefore suggest that **HIV**-1 variants can induce a state of anergy in **HIV**-specific CD4(+) CTLs. Such a mechanism may allow a viral variant to not only **escape** the **CTL** response but also facilitate the persistence of other viral strains that may otherwise be recognized and eliminated by **HIV**-specific CTLs.

L33 ANSWER 41 OF 78 MEDLINE on STN
2000462144. PubMed ID: 11014195. Tat-specific **cytotoxic T lymphocytes** select for SIV **escape** variants during resolution of primary viraemia. Allen T M; O'Connor D H; Jing P; Dzuris J L; Mothe B R; Vogel T U; Dunphy E; Liebl M E; Emerson C; Wilson N; Kunstman K J; Wang X; Allison D B; Hughes A L; Desrosiers R C; Altman J D; Wolinsky S M; Sette A; Watkins D I. (Wisconsin Regional Primate Research Center, University of Wisconsin, Madison 53715-1299, USA.) Nature, (2000 Sep 21) 407 (6802) 386-90. Journal code: 0410462. ISSN: 0028-0836. Pub. country: ENGLAND: United Kingdom. Language: English.

AB **Human immunodeficiency virus** (**HIV**) and simian immunodeficiency virus (SIV) infections are characterized by early peaks of viraemia that decline as strong cellular immune responses develop. Although it has been shown that virus-specific **CD8**-positive **cytotoxic T lymphocytes** (CTLs) exert selective pressure during **HIV** and SIV infection, the data have been controversial. Here we show that Tat-specific **CD8**-positive T-lymphocyte responses select for new viral **escape** variants during the acute phase of infection. We sequenced the entire virus immediately after the acute phase, and found that amino-acid replacements accumulated primarily in Tat **CTL** epitopes. This implies that Tat-specific CTLs may be significantly involved in controlling wild-type virus replication, and suggests that responses against viral proteins that are expressed early during the viral life cycle might be attractive targets for **HIV vaccine** development.

L33 ANSWER 42 OF 78 MEDLINE on STN
2000455140. PubMed ID: 10924089. **Cytotoxic T lymphocyte** responses to **human immunodeficiency virus**: control and **escape**. Sewell A K; Price D A; Oxenius A; Kelleher A D; Phillips R E. (The Nuffield Department of Medicine, John Radcliffe Hospital, Oxford, UK.. asewell@gwmail.jr2.ox.ac.uk) . Stem cells (Dayton, Ohio), (2000) 18 (4) 230-44. Ref: 181. Journal code: 9304532. ISSN: 1066-5099. Pub. country: United States. Language: English.

AB Effective **preventive** and **therapeutic** intervention in individuals exposed to or infected with **human immunodeficiency virus** (**HIV**) depends, in part, on a clear understanding of the interactions between the virus and those elements of the host immune response which control viral replication. Recent advances have provided compelling evidence that **cytotoxic T lymphocytes** (CTLs) constitute an essential component of protective antiretroviral immunity. Here, we review briefly the

significance of this work in the context of previous studies, and outline the mechanisms through which **HIV** evades **CTL** activity.

L33 ANSWER 43 OF 78 MEDLINE on STN
2000269794. PubMed ID: 10807787. Alteration of tumor necrosis factor-alpha T-cell homeostasis following potent antiretroviral **therapy**: contribution to the development of **human immunodeficiency virus**-associated lipodystrophy syndrome. Ledru E; Christeff N; Patey O; de Truchis P; Melchior J C; Gougeon M L. (Unite d'Oncologie Virale, URA CNRS 1930, Departement SIDA et Retrovirus, Institut Pasteur, Paris, France.) Blood, (2000 May 15) 95 (10) 3191-8. Journal code: 7603509. ISSN: 0006-4971. Pub. country: United States. Language: English.

AB Highly-active antiretroviral **therapy** (HAART) has lead to a dramatic decrease in the morbidity of patients infected with the **human immunodeficiency virus** (**HIV**). However, metabolic side effects, including lipodystrophy-associated (LD-associated) dyslipidemia, have been reported in patients treated with antiretroviral **therapy**. This study was designed to determine whether successful HAART was responsible for a dysregulation in the homeostasis of tumor necrosis factor-alpha (TNF-alpha), a cytokine involved in lipid metabolism. Cytokine production was assessed at the single cell level by flow cytometry after a short-term stimulation of peripheral blood T cells from **HIV**-infected (**HIV**(+)) patients who were followed during 18 months of HAART. A dramatic polarization to TNF-alpha synthesis of both CD4 and **CD8** T cells was observed in all patients. Because it was previously shown that TNF-alpha synthesis by T cells was highly controlled by apoptosis, concomitant synthesis of TNF-alpha and priming for apoptosis were also analyzed. The accumulation of T cells primed for TNF-alpha synthesis is related to their **escape** from activation-induced apoptosis, partly due to the cosynthesis of interleukin-2 (IL-2) and TNF-alpha. Interestingly, we observed that LD is associated with a more dramatic TNF-alpha dysregulation, and positive correlations were found between the absolute number of TNF-alpha **CD8** T-cell precursors and lipid parameters usually altered in LD including cholesterol, triglycerides, and the atherogenic ratio apolipoprotein B (apoB)/apoA1. Observations from the study indicate that HAART dysregulates homeostasis of TNF-alpha synthesis and suggest that this proinflammatory response induced by efficient antiretroviral **therapy** is a risk factor of LD development in **HIV**(+) patients.

L33 ANSWER 44 OF 78 MEDLINE on STN
2000265468. PubMed ID: 10807188. Specific recognition of lamivudine-resistant **HIV**-1 by **cytotoxic T lymphocytes**. Schmitt M; Harrer E; Goldwich A; Bauerle M; Graedner I; Kalden J R; Harrer T. (Department of Medicine III with Institute of Clinical Immunology, University of Erlangen-Nurnberg, Erlangen, Germany.) AIDS (London, England), (2000 Apr 14) 14 (6) 653-8. Journal code: 8710219. ISSN: 0269-9370. Pub. country: ENGLAND: United Kingdom. Language: English.

AB OBJECTIVE: The reverse transcriptase (RT) M184V mutation within the HLA-A2-restricted **HIV**-1 **cytotoxic T lymphocyte** (**CTL**) epitope VL9 (VIYQYMDDL; RT 179-187) not only induces drug **escape** against lamivudine but also abolished recognition by a **CTL** clone derived from a long-term non-progressor. To test whether the variant VL9 epitope containing the M184V mutation represents a new **CTL** epitope, we studied recognition of this epitope in a cohort of HLA-A2-positive **HIV**-1-infected patients. METHODS: Peripheral blood mononuclear cells isolated from 28 **HIV**-1-infected patients were stimulated with the peptide VIYQYVDDL, containing the M1 84V mutation. Outgrowing cell lines were tested for specific recognition in a standard chromium-release assay. RESULTS: In one subject, a **CTL** line could be isolated recognizing the peptide VIYQYVDDL in conjunction with HLA-A2. The **CTL** clone also recognized the M1841 mutation, but it failed to recognize the wild-type epitope VIYQYMDDL. CONCLUSION: **CTL** can specifically recognize lamivudine-resistant **HIV**-1 variants. Therefore, the cellular immune response could have an important influence on the control of drug-resistant virus. Furthermore, this demonstrates that the immune system can generate new **CTL** specificities even in patients with advanced

disease, as the M184V **HIV** variants emerges only after drug treatment. Specific immunotherapy against this epitope might be helpful in delaying or **preventing** lamivudine resistance.

L33 ANSWER 45 OF 78 MEDLINE on STN
2000202468. PubMed ID: 10736216. A condition for successful **escape** of a mutant after primary **HIV** infection. Monteiro L H; Goncalves C H; Piqueira J R. (Pos-graduacao-Engenharia Eletrica Rua da Consolacao, Universidade Presbiteriana Mackenzie, n.896, andar 5, Sao Paulo, SP, CEP 01302-907, Brazil.) Journal of theoretical biology, (2000 Apr 21) 203 (4) 399-406. Journal code: 0376342. ISSN: 0022-5193. Pub. country: ENGLAND: United Kingdom. Language: English.

AB **Cytotoxic T lymphocytes** (CTLs) vigorously restrict primary **human immunodeficiency virus** (**HIV**) infection. However, the frequently erroneous process of viral replication favors the creation of mutants not recognizable by primary CTLs. Variants that tolerate the mutations may have selective advantage and may increase in abundance, until the immune system reacts against them. Therefore, such variants represent a way of propagating the viremia. With the aid of a simple mathematical model, here we estimate the intensity of **CTL** cross-reactivity against different strains of **HIV** in a typical progressor. We show that below a critical intensity of cross-reactivity, the concentration of a mutant created at primary peak grows and causes a secondary peak in viremia. Above this critical intensity, such a mutant strain is **prevented** from reaching a detectable level. We speculate about how this result may contribute to the design of an anti-**HIV vaccine**.
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L33 ANSWER 46 OF 78 MEDLINE on STN
2000054202. PubMed ID: 10585898. **Cytotoxic T lymphocytes** and viral evolution in primary **HIV**-1 infection. Price D A; O'callaghan C A; Whelan J A; Easterbrook P J; Phillips R E. (Nuffield Department of Clinical Medicine, John Radcliffe Hospital, Oxford OX3 9DU, U.K.. dprice@worf.molbiol.ox.ac.uk) . Clinical science (London, England : 1979), (1999 Dec) 97 (6) 707-18. Ref: 76. Journal code: 7905731. ISSN: 0143-5221. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Efforts to develop immune-based **therapies** for **HIV** infection have been impeded by incomplete definition of the immunological correlates of protection. Despite many precedents demonstrating that **CD8**(+) **cytotoxic T lymphocytes** are key mediators of protective anti-viral immunity in non-human animal models, direct evidence that these effector cells control viral replication in **HIV**-1 infection has remained elusive. The first part of this paper describes a detailed immunological and genetic study founded on evolutionary considerations. Following infection with **HIV**-1, virus variants which escaped recognition by autologous **cytotoxic T lymphocytes** were shown to possess a selection advantage within the host environment. **Cytotoxic T lymphocytes** therefore exert anti-viral pressure in vivo. This observation provides compelling evidence that **cytotoxic T lymphocytes** comprise a significant element of anti-retroviral immunity. Subsequently, the quantification of peripheral **cytotoxic T lymphocyte** frequencies utilizing peptide-(human leucocyte antigen class I) tetrameric complexes is described. Five patients with qualitatively similar immunodominant **cytotoxic T lymphocyte** responses during symptomatic primary **HIV**-1 infection were studied longitudinally. Expansions of virus-specific **CD8**(+) lymphocytes comprising up to 2% of the total **CD8**(+) T cell population were observed in the acute phase of infection. Antigenic load was identified as an important determinant of circulating **HIV**-1-specific **CD8**(+) lymphocyte levels; however, significant numbers of such cells were also found to persist following prolonged **therapeutic** suppression of plasma viraemia. In addition, an analysis of antigenic sequence variation with time in this case series suggests that the early administration of combination anti-retroviral **therapy** may limit **HIV**-1 mutational **escape** from host cytolytic specificities. The implications of these preliminary data are discussed. The data presented suggest that **vaccination** protocols should aim to elicit vigorous **cytotoxic T**

lymphocyte responses to HIV 1. Attempts to stimulate polyvalent responses to mutationally intolerant epitopes are likely to be most effective. Optimal management of **HIV**-1 infection requires an understanding of dynamic host-virus interactions, and may involve strategies designed to enhance **cytotoxic T lymphocyte** activity following periods of anti-retroviral drug **therapy**.

L33 ANSWER 47 OF 78 MEDLINE on STN
2000027246. PubMed ID: 10559335. Efficient processing of the immunodominant, HLA-A*0201-restricted **human immunodeficiency virus** type 1 **cytotoxic T-lymphocyte** epitope despite multiple variations in the epitope flanking sequences. Brander C; Yang O O; Jones N G; Lee Y; Goulder P; Johnson R P; Trocha A; Colbert D; Hay C; Buchbinder S; Bergmann C C; Zweerink H J; Wolinsky S; Blattner W A; Kalams S A; Walker B D. (AIDS Research Center and Infectious Disease Unit, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts 02114, USA.. brander@helix.mgh.harvard.edu) . Journal of virology, (1999 Dec) 73 (12) 10191-8. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Immune **escape** from **cytotoxic T-lymphocyte** (**CTL**) responses has been shown to occur not only by changes within the targeted epitope but also by changes in the flanking sequences which interfere with the processing of the immunogenic peptide. However, the frequency of such an **escape** mechanism has not been determined. To investigate whether naturally occurring variations in the flanking sequences of an immunodominant **human immunodeficiency virus** type 1 (**HIV**-1) Gag **CTL** epitope **prevent** antigen processing, cells infected with **HIV**-1 or **vaccinia** virus constructs encoding different patient-derived Gag sequences were tested for recognition by HLA-A*0201-restricted, p17-specific **CTL**. We found that the immunodominant p17 epitope (SL9) and its variants were efficiently processed from minigene expressing vectors and from six **HIV**-1 Gag variants expressed by recombinant **vaccinia** virus constructs. Furthermore, SL9-specific **CTL** clones derived from multiple donors efficiently inhibited virus replication when added to HLA-A*0201-bearing cells infected with primary or laboratory-adapted strains of virus, despite the variability in the SL9 flanking sequences. These data suggest that **escape** from this immunodominant **CTL** response is not frequently accomplished by changes in the epitope flanking sequences.

L33 ANSWER 48 OF 78 MEDLINE on STN
2000023408. PubMed ID: 10560752. Mechanisms of **human immunodeficiency virus** type 1 inhibition by hydroxyurea. Lori F; Lisziewicz J. (Research Institute for Genetic and Human Therapy, Washington, DC, USA.. RIGHT@gunet.georgetown.edu) . Journal of biological regulators and homeostatic agents, (1999 Jul-Sep) 13 (3) 176-80. Ref: 40. Journal code: 8809253. ISSN: 0393-974X. Pub. country: Italy. Language: English.

AB Virus life cycles depend on cellular factors. Therefore, targeting cellular in combination with viral enzymes could be an effective control in virus replication. In contrast to viral proteins, cellular proteins are not prone to mutations; therefore, viral **escape** is not expected from drugs inhibiting cellular factors. Hydroxyurea inhibits the cellular enzyme ribonucleotide reductase, thus reducing DNA synthesis. Furthermore, this drug potentiates the activity of nucleoside analogues, inhibits the **escape** of A-analogue resistant mutants, and increases the phosphorylation of T-analogues. Besides its antiviral activity, hydroxyurea effects the immune system by decreasing immune activation, inhibiting the expansion of **CD8** cells and the depletion of CD4 cells. Hydroxyurea has been used in medicine for 40 years, is well tolerated, and it is the least expensive available anti-**HIV**-1 drug. These characteristics make hydroxyurea a primary candidate for use in combination **therapies** for the treatment of **HIV**-1 infection.

L33 ANSWER 49 OF 78 MEDLINE on STN
2000015190. PubMed ID: 10545993. Virus-specific **cytotoxic** **T-lymphocyte** responses select for amino-acid variation in simian

immunodeficiency virus Env and Nef. Evans D T; O'Connor D H; Jing P; Dzuris J L; Sidney J; da Silva J; Allen T M; Horton H; Venham J E; Rudersdorf R A; Vogel T; Pauza C D; Bontrop R E; DeMars R; Sette A; Hughes A L; Watkins D I. (Wisconsin Regional Primate Research Center, University of Wisconsin, 1220 Capitol Court, Madison, Wisconsin 53715, USA.) Nature medicine, (1999 Nov) 5 (11) 1270-6. Journal code: 9502015. ISSN: 1078-8956. Pub. country: United States. Language: English.

AB **Cytotoxic T-lymphocyte** (**CTL**) responses to **human immunodeficiency virus** arise early after infection, but ultimately fail to **prevent** progression to AIDS. **Human immunodeficiency virus** may evade the **CTL** response by accumulating amino-acid replacements within **CTL** epitopes. We studied 10 **CTL** epitopes during the course of simian immunodeficiency virus disease progression in three related macaques. All 10 of these **CTL** epitopes accumulated amino-acid replacements and showed evidence of positive selection by the time the macaques died. Many of the amino-acid replacements in these epitopes reduced or eliminated major histocompatibility complex class I binding and/or **CTL** recognition. These findings strongly support the **CTL** '**escape**' hypothesis.

L33 ANSWER 50 OF 78 MEDLINE on STN

1999323981. PubMed ID: 10395680. The antiviral activity of **HIV**-specific **CD8**+ **CTL** clones is limited by elimination due to encounter with **HIV**-infected targets. McKinney D M; Lewinsohn D A; Riddell S R; Greenberg P D; Mosier D E. (Department of Immunology, Scripps Research Institute, La Jolla, CA 92037, USA.) Journal of immunology (Baltimore, Md. : 1950), (1999 Jul 15) 163 (2) 861-7. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB Adoptive immunotherapy of virus infection with viral-specific **CTL** has shown promise in animal models and human virus infections and is being evaluated as a **therapy** for established **HIV**-1 infection. Defining the individual obstacles for success is difficult in human trials. We have therefore examined the localization, persistence, and antiviral activity of **HIV**-1 gag-specific **CTL** clones in both **HIV**-1-infected and uninfected haplotype-matched human (hu)-PBL-SCID mice. Injection of gag-specific clones but not control **CTL** into **HIV**-1-infected hosts reduced plasma viremia by >10-fold but failed to eliminate the virus infection from most treated animals. The failure to eradicate virus did not reflect selection of **escape** variants because the gag epitope remained unmutated in virus isolates obtained after **CTL therapy**. Injection of carboxyfluorescein diacetate succinimide ester-labeled **CTL** demonstrated markedly different fates for gag-specific **CTL** in the presence or absence of **HIV**-1 infection. **HIV**-1-specific **CTL** rapidly disappeared in infected recipients, whereas they were maintained at high numbers in uninfected mice. By contrast, control **CTL** were long lived in both infected and uninfected recipients. Thus, interaction of **CTL** with virus-infected target cells in vivo leads not only to target destruction but also to the rapid disappearance of the infused **CTL**, and it limits the capacity of **CTL therapy** to eliminate **HIV**-1 infection.

L33 ANSWER 51 OF 78 MEDLINE on STN

1999316303. PubMed ID: 10384115. A model for **CD8**+ **CTL** tumor immunosurveillance and regulation of tumor **escape** by CD4 T cells through an effect on quality of **CTL**. Matsui S; Ahlers J D; Vortmeyer A O; Terabe M; Tsukui T; Carbone D P; Liotta L A; Berzofsky J A. (Molecular Immunogenetics and Vaccine Research Section, Metabolism Branch, Laboratory of Pathology, National Cancer Institute, Bethesda, MD 20892, USA.) Journal of immunology (Baltimore, Md. : 1950), (1999 Jul 1) 163 (1) 184-93. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB Understanding immune mechanisms influencing cancer regression, recurrence, and metastasis may be critical to developing effective immunotherapy. Using a tumor expressing **HIV** gp160 as a model viral tumor Ag, we found a growth-regression-recurrence pattern, and used this to investigate mechanisms of immunosurveillance. Regression was dependent on **CD8** T cells, and recurrent tumors were resistant to **CTL**, had substantially

reduced expression of epitope mRNA, but retained the gp160 gene, MHC, and processing apparatus. Increasing **CTL** numbers by advance priming with **vaccinia** virus expressing gp160 **prevented** only the initial tumor growth but not the later appearance of **escape** variants. Unexpectedly, CD4 cell depletion protected mice from tumor recurrence, whereas IL-4 knockout mice, deficient in Th2 cells, did not show this protection, and IFN-gamma knockout mice were more susceptible. Purified **CD8** T cells from CD4-depleted mice following tumor regression had more IFN-gamma mRNA and lysed tumor cells without stimulation ex vivo, in contrast to CD4-intact mice. Thus, the quality as well as quantity of **CD8+ CTL** determines the completeness of immunosurveillance and is controlled by CD4 T cells but not solely Th2 cytokines. This model of immunosurveillance may indicate ways to enhance the efficacy of surveillance and improve immunotherapy.

L33 ANSWER 52 OF 78 MEDLINE on STN
1999292843. PubMed ID: 10364299. Lack of viral **escape** and defective in vivo activation of **human immunodeficiency virus** type 1-specific **cytotoxic T lymphocytes** in rapidly progressive infection. Hay C M; Ruhl D J; Basgoz N O; Wilson C C; Billingsley J M; DePasquale M P; D'Aquila R T; Wolinsky S M; Crawford J M; Montefiori D C; Walker B D. (Partners AIDS Research Center and Infectious Disease Unit, Massachusetts General Hospital, Boston, Massachusetts 02114, USA.) Journal of virology, (1999 Jul) 73 (7) 5509-19. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB **Human immunodeficiency virus** type 1 (**HIV**-1)-specific immune responses over the course of rapidly progressive infection are not well defined. Detailed longitudinal analyses of neutralizing antibodies, lymphocyte proliferation, in vivo-activated and memory **cytotoxic T-lymphocyte** (**CTL**) responses, and viral sequence variation were performed on a patient who presented with acute **HIV**-1 infection, developed an AIDS-defining illness 13 months later, and died 45 months after presentation. Neutralizing-antibody responses remained weak throughout, and no **HIV**-1-specific lymphocyte proliferative responses were seen even early in the disease course. Strong in vivo-activated **CTL** directed against Env and Pol epitopes were present at the time of the initial drop in viremia but were quickly lost. Memory **CTL** against Env and Pol epitopes were detected throughout the course of infection; however, these **CTL** were not activated in vivo. Despite an initially narrow **CTL** response, new epitopes were not targeted as the disease progressed. Viral sequencing showed the emergence of variants within the two targeted **CTL** epitopes; however, viral variants within the immunodominant Env epitope were well recognized by **CTL**, and there was no evidence of viral **escape** from immune system detection within this epitope. These data demonstrate a narrowly directed, static **CTL** response in a patient with rapidly progressive disease. We also show that disease progression can occur in the presence of persistent memory **CTL** recognition of autologous epitopes and in the absence of detectable **escape** from **CTL** responses, consistent with an in vivo defect in activation of **CTL**.

L33 ANSWER 53 OF 78 MEDLINE on STN
1999292822. PubMed ID: 10364278. Immunogenicity of a **human immunodeficiency virus** (**HIV**) polytope **vaccine** containing multiple HLA A2 **HIV CD8**(+) **cytotoxic T-cell** epitopes. Woodberry T; Gardner J; Mateo L; Eisen D; Medveczky J; Ramshaw I A; Thomson S A; Ffrench R A; Elliott S L; Firat H; Lemonnier F A; Suhrbier A. (Australian Centre for International & Tropical Health & Nutrition, Cooperative Research Centre for Vaccine Technology, Queensland Institute of Medical Research, Brisbane, Australia.) Journal of virology, (1999 Jul) 73 (7) 5320-5. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Compelling evidence now suggests that alphabeta **CD8 cytotoxic T lymphocytes** (**CTL**) have an important role in **preventing human immunodeficiency virus** (**HIV**) infection and/or slowing progression to AIDS. Here, we describe an **HIV** type 1 **CTL** polyepitope, or polytope,

vaccine comprising seven contiguous minimal HLA A2 restricted **CD8** **CTL** epitopes conjoined in a single artificial construct. Epitope-specific **CTL** lines derived from **HIV**-infected individuals were able to recognize every epitope within the construct, and HLA A2-transgenic mice immunized with a recombinant virus **vaccine** coding for the **HIV** polytope also generated **CTL** specific for different epitopes. Each epitope in the polytope construct was therefore processed and presented, illustrating the feasibility of the polytope approach for **HIV** **vaccine** design. By simultaneously inducing **CTL** specific for different epitopes, an **HIV** polytope **vaccine** might generate activity against multiple challenge isolates and/or preempt the formation of **CTL escape** mutants.

L33 ANSWER 54 OF 78 MEDLINE on STN
1999214336. PubMed ID: 10196293. Frequent detection of **escape** from **cytotoxic T-lymphocyte** recognition in perinatal **human immunodeficiency virus** (**HIV**) type 1 transmission: the ariel project for the **prevention** of transmission of **HIV** from mother to infant. Wilson C C; Brown R C; Korber B T; Wilkes B M; Ruhl D J; Sakamoto D; Kunstman K; Luzuriaga K; Hanson I C; Widmayer S M; Wiznia A; Clapp S; Ammann A J; Koup R A; Wolinsky S M; Walker B D. (AIDS Research Center and Infectious Disease Unit, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts 02114, USA.) Journal of virology, (1999 May) 73 (5) 3975-85. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Host immunologic factors, including **human immunodeficiency virus** (**HIV**)-specific **cytotoxic T lymphocytes** (**CTL**), are thought to contribute to the control of **HIV** type 1 (**HIV**-1) replication and thus delay disease progression in infected individuals. Host immunologic factors are also likely to influence perinatal transmission of **HIV**-1 from infected mother to infant. In this study, the potential role of **CTL** in modulating **HIV**-1 transmission from mother to infant was examined in 11 **HIV**-1-infected mothers, 3 of whom transmitted virus to their offspring. Frequencies of **HIV**-1-specific human leukocyte antigen class I-restricted **CTL** responses and viral epitope amino acid sequence variation were determined in the mothers and their infected infants. Maternal **HIV**-1-specific **CTL** clones were derived from each of the **HIV**-1-infected pregnant women. Amino acid substitutions within the targeted **CTL** epitopes were more frequently identified in transmitting mothers than in nontransmitting mothers, and immune **escape** from **CTL** recognition was detected in all three transmitting mothers but in only one of eight nontransmitting mothers. The majority of viral sequences obtained from the **HIV**-1-infected infant blood samples were susceptible to maternal **CTL**. These findings demonstrate that epitope amino acid sequence variation and **escape** from **CTL** recognition occur more frequently in mothers that transmit **HIV**-1 to their infants than in those who do not. However, the transmitted virus can be a **CTL** susceptible form, suggesting inadequate in vivo immune control.

L33 ANSWER 55 OF 78 MEDLINE on STN
1999203068. PubMed ID: 10189185. **Cytotoxic T-lymphocyte** responses to **HIV**-1 reverse transcriptase (review). Menendez-Arias L; Mas A; Domingo E. (Centro de Biologia Molecular "Severo Ochoa", CSIC-Universidad Autonoma de Madrid, Cantoblanco, Spain.) Viral immunology, (1998) 11 (4) 167-81. Ref: 81. Journal code: 8801552. ISSN: 0882-8245. Pub. country: United States. Language: English.

AB **Cytotoxic T lymphocytes** (**CTL**) play an important role in the control of **human immunodeficiency virus** (**HIV**) infection. **CTL** responses have been demonstrated for most of the **HIV** gene products, predominantly gag, pol, and env-encoded proteins, and also for the regulatory proteins Nef, Tat, Vif, or Rev. The **HIV**-1 reverse transcriptase (RT), which derives from expression of the pol gene, is an important target of cellular immune responses in infected individuals. More than 40 different peptides containing RT-specific **CTL** epitopes have been identified. The most conserved and frequently detected are located in the 'fingers' and 'palm' subdomains of the enzyme, but other epitopes

have been found in the thumb and connection subdomains as well as in the RNase H domain. Studies on the sequence variability and functional role of amino acids forming **CTL** epitopes are relevant for addressing important questions relative to viral **escape** from immmune control and the future design of anti-AIDS **vaccines**.

L33 ANSWER 56 OF 78 MEDLINE on STN
1998442699. PubMed ID: 9771756. **Vaccine**-induced **cytotoxic T lymphocytes** protect against retroviral challenge. Hislop A D; Good M F; Mateo L; Gardner J; Gatei M H; Daniel R C; Meyers B V; Lavin M F; Suhrbier A. (The Co-operative Research Centre for Vaccine Technology, The Queensland Institute of Medical Research, PO Royal Brisbane Hospital, Australia.) Nature medicine, (1998 Oct) 4 (10) 1193-6. Journal code: 9502015. ISSN: 1078-8956. Pub. country: United States. Language: English.

AB The development of prophylactic **vaccines** against retroviral diseases has been impeded by the lack of obvious immune correlates for protection. **Cytotoxic T-lymphocyte** (**CTL**), CD4-lymphocyteS, chemokine and/or antibody responses have all been associated with protection against **HIV** and AIDS; however, effective and safe **vaccination** strategies remain elusive. Here we show that **vaccination** with a minimal ovine **CTL** peptide epitope identified within gp51 of the retrovirus bovine leukemia virus (BLV), consistently induced peptide-specific CTLs. Only sheep whose CTLs were also capable of recognizing retrovirus-infected cells were fully protected when challenged with BLV. This retrovirus displays limited sequence variation; thus, in the relative absence of confounding **CTL escape** variants, virus-specific CTLs targeting a single epitope were able to **prevent** the establishment of a latent retroviral infection.

L33 ANSWER 57 OF 78 MEDLINE on STN
1998393726. PubMed ID: 9724785. beta-chemokines and neutralizing antibody titers correlate with sterilizing immunity generated in **HIV**-1 **vaccinated** macaques. Heeney J L; Teeuwsen V J; van Gils M; Bogers W M; De Giuli Morghen C; Radaelli A; Barnett S; Morein B; Akerblom L; Wang Y; Lehner T; Davis D. (Department of Virology, Biomedical Primate Research Centre, Lange Kleiweg 157, 2288 GJ, Rijswijk, The Netherlands.) Proceedings of the National Academy of Sciences of the United States of America, (1998 Sep 1) 95 (18) 10803-8. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB One of the obstacles to AIDS **vaccine** development is the variability of **HIV**-1 within individuals and within infected populations, enabling viral **escape** from highly specific **vaccine** induced immune responses. An understanding of the different immune mechanisms capable of inhibiting **HIV** infection may be of benefit in the eventual design of **vaccines** effective against **HIV**-1 variants. To study this we first compared the immune responses induced in Rhesus monkeys by using two different immunization strategies based on the same **vaccine** strain of **HIV**-1. We then utilized a chimeric simian/**HIV** that expressed the envelope of a dual tropic **HIV**-1 **escape** variant isolated from a later time point from the same patient from which the **vaccine** strain was isolated. Upon challenge, one **vaccine** group was completely protected from infection, whereas all of the other **vaccinees** and controls became infected. Protected macaques developed highest titers of heterologous neutralizing antibodies, and consistently elevated **HIV**-1-specific T helper responses. Furthermore, only protected animals had markedly increased concentrations of RANTES, macrophage inflammatory proteins 1alpha and 1beta produced by circulating **CD8**(+) T cells. These results suggest that **vaccine** strategies that induce multiple effector mechanisms in concert with beta-chemokines may be desired in the generation of protective immune responses by **HIV**-1 **vaccines**.

L33 ANSWER 58 OF 78 MEDLINE on STN
1998325206. PubMed ID: 9658134. Kinetics of antiviral activity by **human immunodeficiency virus** type 1-specific **cytotoxic T lymphocytes** (**CTL**) and rapid selection of **CTL escape** virus in vitro. Van Baalen C A; Schutten M; Huisman R C; Boers P H; Gruters R A; Osterhaus A D. (Institute of Virology, Erasmus University, Rotterdam, The Netherlands.)

Journal of virology, (1998 Aug) 72 (8) 6651-7. Journal code: 0113724.
ISSN: 0022-538X. Pub. country: United States. Language: English.

AB The antiviral activity of a **CD8**(+) **cytotoxic T-lymphocyte** (**CTL**) clone (TCC108) directed against a newly identified HLA-B14-restricted epitope, **human immunodeficiency virus** type 1 (**HIV**-1) Rev(67-75) SAEPVPLQL, was analyzed with respect to its kinetics of target cell lysis and inhibition of **HIV**-1 production. Addition of TCC108 cells or **CD8**(+) reverse transcriptase-specific CTLs to HLA-matched CD4(+) T cells at different times after infection with **HIV**-1 IIIB showed that infected cells became susceptible to **CTL**-mediated lysis before peak virus production but after the onset of progeny virus release. When either of these CTLs were added to part of the infected cells immediately after infection, p55 expression and virus production were significantly suppressed. These data support a model in which CTLs, apart from exerting cytolytic activity which may **prevent** continued virus release, can interfere with viral protein expression during the eclipse phase via noncytolytic mechanisms. TCC108-mediated inhibition of virus replication in peripheral blood mononuclear cells caused rapid selection of a virus with a mutation (69E-->K) in the Rev(67-75) **CTL** epitope which abolished recognition by TCC108 cells. Taken together, these data suggest that both cytolytic and noncytolytic antiviral mechanisms of CTLs can be specifically targeted to **HIV**-1-infected cells.

L33 ANSWER 59 OF 78 MEDLINE on STN
1998214891. PubMed ID: 9554272. Induction of a TH1 type cellular immune response to the human immunodeficiency type 1 virus by in vivo DNA inoculation. Boyer J; Ugen K; Wang B; Chattergoon M; Tsai A; Merva M; Weiner D B. (Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, USA.) Developments in biological standardization, (1998) 92 169-74. Journal code: 0427140. ISSN: 0301-5149. Pub. country: Switzerland. Language: English.

AB DNA inoculation is capable of producing antigens intracellularly for ultimate presentation to the cellular and humoral components of the immune system and has potential for **vaccine** strategies against a number of infectious pathogens including **HIV**-1. It is well documented that the antigenic diversity of **HIV**-1 and its high level of nucleotide mutations during reverse transcription can lead to **escape** from immune surveillance. However, data suggest that a **CD8**-mediated **cytotoxic T lymphocyte** response may be less susceptible to **escape** mutants. We have shown previously that in vivo inoculation of rodents and non-human primates with plasmid expression vectors encoding **HIV**-1 gene products leads to production of **HIV**-1 antigens and results in the production of both cellular and humoral immune responses. In addition we have also demonstrated previously that these responses lead to protection in several in vivo models. We further demonstrate here that the cellular response induced is a type TH1 response and specific lysis of **HIV**-infected targets is **CD8**-mediated.

L33 ANSWER 60 OF 78 MEDLINE on STN
1998105786. PubMed ID: 9445041. Selection of virus variants and emergence of virus **escape** mutants after immunization with an epitope **vaccine**. Mortara L; Letourneur F; Gras-Masse H; Venet A; Guillet J G; Bourgault-Villada I. (Laboratoire d'Immunologie des Pathologies Infectieuses et Tumorales, INSERM U445, Paris, France.. mortara@icgm.cochin.inserm.fr) . Journal of virology, (1998 Feb) 72 (2) 1403-10. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB In this report, we assessed the evolution of the **cytotoxic T-lymphocyte** (**CTL**) response induced by an epitope **vaccine**. In two macaques immunized with a mixture of lipopeptides derived from simian immunodeficiency virus (SIV) Nef and Gag proteins, **CTL** responses were directed against the same, single epitope of the Nef protein (amino acids 128 to 137) presenting an alanine at position 136 (Nef 128-137/136A). However, after 5 months of SIV infection, peripheral blood mononuclear cells from both macaques lost their ability to be stimulated by autologous SIV-infected cells while still retaining their capacity to generate

cytotoxic responses after specific Nef 128-137/136A peptide stimulation. The sequences of the pathogenic viral isolate used for the challenge showed a mixture of several variants. Within the Nef epitopic sequence from amino acids 128 to 137, 82% of viral variants expressed the epitopic peptide Nef 128-137/136A; the remaining variants presented a threonine at position 136 (Nef 128-137/136T). In contrast, sequence analysis of cloned proviral DNA obtained from both macaques 5 months after SIV challenge showed a different pattern of quasi-species variants; 100% of clones presented a threonine at position 136 (Nef 128-137/136T), suggesting the disappearance of viral variants with an alanine at this position under antiviral pressure exerted by Nef 128-137/136A-specific CTLs. In addition, 12 months after SIV challenge, six of eight clones from one macaque presented a glutamic acid at position 131 (Nef 128-137/131E+136T), which was not found in the infecting isolate. Furthermore, CTLs generated very early after SIV challenge were able to lyse cells sensitized with the Nef 128-137/136A epitope. In contrast, lysis was significantly less effective or even did not occur when either the selected peptide Nef 128-137/136T or the **escape** variant peptide Nef 128-137/131E+136T was used in a target cell sensitization assay. Dose analysis of peptides used to sensitize target cells as well as a major histocompatibility complex (MHC)-peptide stability assay suggested that the selected peptide Nef 128-137/136T has an altered capacity to bind to the MHC. These data suggest that **CTL** pressure leads to the selection of viral variants and to the emergence of **escape** mutants and supports the fact that immunization should elicit broad **CTL** responses.

L33 ANSWER 61 OF 78 MEDLINE on STN
1998078460. PubMed ID: 9416500. Co-evolution of **human immunodeficiency virus** and **cytotoxic T-lymphocyte** responses. Goulder P; Price D; Nowak M; Rowland-Jones S; Phillips R; McMichael A. (Nuffield Department of Clinical Medicine, University of Oxford, John Radcliffe Hospital, UK.) Immunological reviews, (1997 Oct) 159 17-29. Ref: 91. Journal code: 7702118. ISSN: 0105-2896. Pub. country: Denmark. Language: English.

AB After more than a decade of intensive research, the precise role of **human immunodeficiency virus** (HIV)-specific **cytotoxic T lymphocytes** (**CTL**) in determining the course of the infection remains open to argument. It is established that **HIV**-specific **CTL** appear early in the infection and are temporally associated with the clearance of culturable virus from the blood; that **CTL** are generally detectable at very high levels throughout the asymptomatic phase and decline at the time of progression to AIDS; and that **CTL**-mediated killing is sufficiently fast to **prevent** production of new virions by **HIV**-infected cells. However, viral turnover is high throughout the course of the infection, and infected individuals progress inexorably to disease in spite of the **CTL** response. In order to address the question of whether **CTL** play an active part in influencing the course of **HIV** infection, one approach has been to seek evidence for **CTL**-mediated selection pressure on the virus. Several clear examples of **CTL** epitope-specific mutations selected to fixation are described. We argue that **CTL escape** is a common event which occurs at all stages of the infection. Detailed longitudinal studies are required to detect **CTL escape** and to understand the complexities contributed by factors such as a polyvalent **CTL** response and the presence of epitope variants which antagonise the **CTL** response. In conclusion, there is strong evidence of a dynamic process in which **CTL** impose important selection constraints upon **HIV** from which the virus attempts to **escape**; ultimately, at the time of disease progression, the tenuous control of **CTL** over the virus is lost.

L33 ANSWER 62 OF 78 MEDLINE on STN
97470992. PubMed ID: 9326635. Lysis of **HIV**-1-infected cells and inhibition of viral replication by universal receptor T cells. Yang O O; Tran A C; Kalams S A; Johnson R P; Roberts M R; Walker B D. (AIDS Research Center and Infectious Disease Unit, Massachusetts General Hospital and Harvard Medical School, Charlestown, MA 02129, USA.) Proceedings of the National Academy of Sciences of the United States of America, (1997 Oct 14) 94 (21) 11478-83. Journal code: 7505876. ISSN: 0027-8424. Pub.

Country: United States. Language: English.

AB Increasing evidence suggests that **HIV**-1-specific **cytotoxic T lymphocytes** (CTLs) are a key host immune response to **HIV**-1 infection. Generation of **CTL** responses for **prevention** or **therapy** of **HIV**-1 infection has several intrinsic technical barriers such as antigen expression and presentation, the varying HLA restrictions between different individuals, and the potential for viral **escape** by sequence variation or surface molecule alteration on infected cells. A strategy to circumvent these limitations is the construction of a chimeric T cell receptor containing human CD4 or **HIV**-1-specific Ig sequences linked to the signaling domain of the T cell receptor zeta chain (universal T cell receptor). **CD8**+ CTLs transduced with this universal receptor can then bind and lyse infected cells that express surface **HIV**-1 gp120. We evaluated the ability of universal-receptor-bearing **CD8**+ cells from a seronegative donor to lyse acutely infected cells and inhibit **HIV**-1 replication in vitro. The kinetics of lysis and efficiency of inhibition were comparable to that of naturally occurring **HIV**-1-specific **CTL** clones isolated from infected individuals. Further study will be required to determine the utility of these cells as a **therapeutic** strategy in vivo.

L33 ANSWER 63 OF 78 MEDLINE on STN

97411686. PubMed ID: 9266632. Characteristics of the intrahepatic **cytotoxic T lymphocyte** response in chronic hepatitis C virus infection. Koziel M J; Walker B D. (Infectious Disease Division, Beth Israel Deaconess Medical Ctr., Boston, MA 02215, USA.) Springer seminars in immunopathology, (1997) 19 (1) 69-83. Ref: 90. Journal code: 7910384. ISSN: 0344-4325. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB Based on our **CTL** studies of over 44 persons with chronic HCV infection, we are able to arrive at a number of conclusions. Clearly this cellular immune response is heterogeneous among infected persons. We have not identified any specific HCV protein which appears to be immunodominant for **CTL** responses, but rather we have detected diverse responses to both structural and non-structural proteins. Using an identical stimulation strategy for all persons studied, we have been able to detect responses in only approximately one third of persons with chronic infection. Among these persons, the responses among liver-infiltrating lymphocytes are greater than those detected in fresh peripheral blood, suggesting that the **CTL** are homing to the site of maximal viral burden in these persons. Some viral proteins contain overlapping epitopes presented by more than one HLA class I molecule, and we have also found cases where peptides in the same HLA superfamily, such as the HLA A3 superfamily which contains A11, for which the same peptide can be presented by both alleles (manuscript in preparation). Although sequence variation between the infecting strain and the **vaccinia** constructs used to test for responses may lead to non-recognition of some variants, even the highly conserved core protein appears to be an inconsistent and actually infrequent target for detectable **CTL** responses. The magnitude of the **CTL** response appears to vary greatly, from being undetectable to being so vigorous that it an be detected in stimulated peripheral blood. The breadth of the response also varies widely, ranging from the detection of a response to a single epitope in some persons, to the simultaneous recognition of up to five different epitopes in others. Even in persons of the same HLA type, we have not seen consistent targeting of the same epitopes except in rare cases. Despite the detection of over 20 epitopes and their restricting class I alleles using CTR derived from liver-infiltrating lymphocytes, we have identified only one epitope that has been shown to be targeted by more than one person of the same HLA type. These findings lead us to speculate that the **CTL** response may be submaximal in the majority of infected persons. The reasons for this are presently obscure, but could relate to a number of factors. The epitopes targeted are found within variable regions of the virus, such that immune **escape** from established **CTL** responses has to be considered a real possibility. Sequence variation may also lead to antagonism of **CTL** responses, as has been demonstrated for both **HIV** and HBV infections. Furthermore, sequence variation either within or adjacent to regions containing **CTL** epitopes

can lead to altered antigen processing, either due to alteration of proteolytic processing of the viral peptides in the cytoplasm or to altered transport and altered association with class I molecules. A number of issues regarding the **CTL** response in HCV infection still require substantial attention. The apparent inability of **CTL** to clear this virus needs to be addressed, as does the potential role for viral immunomodulatory molecules in HCV persistence. Although we and others have shown **CTL** responses to be present in persons with chronic infection, the role of **CTL** in acute HCV infection needs to be determined. The best studied chronic human viral infection is **HIV** infection, in which expanding data indicate that the early events following primary infection predict the subsequent course of illness. Viral load in the first 1-2 years after infection is highly predictive of the subsequent disease course in **HIV** infection, and recent experimental data in humans suggest that early immune responses may be predictive of subsequent disease course. Such studies in HCV infection have been difficult to achieve, since primary HCV infection is often asymptomatic, and transfusion-related cases are now rare. (ABSTRACT TRUNCATED)

L33 ANSWER 64 OF 78 MEDLINE on STN
97391105. PubMed ID: 9247912. A hypothesis to explain the role of the suppressor and helper T cells in the immunologic selection of highly related **human immunodeficiency virus** isolates found in infected patients. Barnett E; Barnett N. (Department of Medicine, University of Southern California School of Medicine, Los Angeles, USA.) Medical hypotheses, (1997 Jul) 49 (1) 77-9. Journal code: 7505668. ISSN: 0306-9877. Pub. country: ENGLAND: United Kingdom. Language: English.

AB It is proposed that specific **human immunodeficiency virus** determinants in seropositive individuals are capable of evoking very strong suppressor T cell responses which inactivate certain helper T cells. This helper T cell suppression may be sufficient to inhibit the **cytotoxic T cell** recognition of these specific retroviral antigens and significantly reduce neutralizing antibody titers. As a consequence of the poor T helper cell responses to these different antigens, a number of related **human immunodeficiency virus** isolates are able to **escape** immune surveillance over the entire course of the infection. The selection and persistence of these distinct but related viral isolates may allow the **human immunodeficiency virus** infection to progress to other tissues and contribute to the gradual destruction of the remaining helper T cell population. Thus, the development of an effective antiviral **therapy** and possibly even a cure for the acquired immune deficiency syndrome may depend on the management of the suppressor and helper T cell activity in the infected individual.

L33 ANSWER 65 OF 78 MEDLINE on STN
97304244. PubMed ID: 9160516. A chain section containing epitopes for cytotoxic T, B and helper T cells within a highly conserved region found in the **human immunodeficiency virus** type 1 Gag protein. Nakamura Y; Kameoka M; Tobiume M; Kaya M; Ohki K; Yamada T; Ikuta K. (Section of Serology, Institute of Immunological Science, Hokkaido University, Sapporo, Japan.) Vaccine, (1997 Apr) 15 (5) 489-96. Journal code: 8406899. ISSN: 0264-410X. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Cell-mediated immune responses constitute a major defense against the spread of **human immunodeficiency virus** type 1 (**HIV**-1). However, multiple alterations within a particular epitope may accumulate during disease progression, allowing the virus to **escape cytotoxic T lymphocytes** (CTLs). Therefore, the best candidate for a peptide **vaccine** that would **prevent** the onset of the disease might be a chain section containing epitopes for the generation of CTLs in regions of conserved sequences among different **HIV**-1 isolates. We previously showed that immunizing mice with synthetic peptides consisting of 23-amino acids (Gag-23mer; 287-309 amino acid residues) in a highly conserved region derived from the major core protein p24 of **HIV**-1 generates specific CTLs as well as antibodies. Here, we identified one **CTL** (T-1; 291-300) and two B-cell (B-1; 290-299 and B-2; 300-309) epitopes, all of

which consisted of 10 amino acids within the region. In addition, helper T cells primed by the Gag-23mer peptide were proliferated by in vitro stimulation with a 21mer (H-1; 289-309) or a 19mer (H-2; 291-309) peptide, but not with a 17mer peptide (293-309) or 19mer peptide (287-305). Immunization with the H-1 peptide generated an antibody reactive to B-1, but not B-2, whereas that with H-2 generated an antibody reactive to B-2, but not B-1. CTLs were not generated by immunization with these peptides, indicating that the entire sequence of Gag-23mer is the helper epitope for CTLs. Thus, the Gag-23mer is a chain section containing epitopes for cytotoxic T, B and helper T-cells within a highly conserved region of **HIV**-1 Gag protein.

L33 ANSWER 66 OF 78 MEDLINE on STN
97170967. PubMed ID: 9018240. Antiviral pressure exerted by **HIV**-1-specific **cytotoxic T lymphocytes** (CTLs) during primary infection demonstrated by rapid selection of **CTL escape** virus. Borrow P; Lewicki H; Wei X; Horwitz M S; Peffer N; Meyers H; Nelson J A; Gairin J E; Hahn B H; Oldstone M B; Shaw G M. (Department of Neuropharmacology, Scripps Research Institute, La Jolla, California 92037, USA.) Nature medicine, (1997 Feb) 3 (2) 205-11. Journal code: 9502015. ISSN: 1078-8956. Pub. country: United States. Language: English.

AB The **HIV**-1-specific **cytotoxic T lymphocyte** (**CTL**) response is temporally associated with the decline in viremia during primary **HIV**-1 infection, but definitive evidence that it is of importance in virus containment has been lacking. Here we show that in a patient whose early **CTL** response was focused on a highly immunodominant epitope in gp 160, there was rapid elimination of the transmitted virus strain and selection for a virus population bearing amino acid changes at a single residue within this epitope, which conferred **escape** from recognition by epitope-specific **CTL**. The magnitude (> 100-fold), kinetics (30-72 days from onset of symptoms) and genetic pathways of virus **escape** from **CTL** pressure were comparable to virus **escape** from antiretroviral **therapy**, indicating the biological significance of the **CTL** response in vivo. One aim of **HIV**-1 **vaccines** should thus be to elicit strong **CTL** responses against multiple codominant viral epitopes.

L33 ANSWER 67 OF 78 MEDLINE on STN
97146051. PubMed ID: 8992998. Antagonism of **vaccine**-induced **HIV**-1-specific CD4+ T cells by primary **HIV**-1 infection: potential mechanism of **vaccine** failure. Kent S J; Greenberg P D; Hoffman M C; Akridge R E; McElrath M J. (Department of Medicine, University of Washington School of Medicine, Seattle 98145, USA.) Journal of immunology (Baltimore, Md. : 1950), (1997 Jan 15) 158 (2) 807-15. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB Prior immunity to **HIV**-1 elicited by **vaccination** may modify subsequent responses upon exposure to infectious **HIV**-1. An **HIV**-1-uninfected person entered in a **vaccine** trial that included immunizations to **HIV**-1(LAI) envelope with a recombinant **vaccinia** vector and recombinant protein developed envelope-specific CD4+ T cell responses, including proliferative and cytolytic responses, but was not protected from a high risk **HIV**-1 exposure. CD4+ T cell clones derived from blood at the peak of **vaccine**-induced immunity recognized and lysed autologous target cells expressing four distinct regions within the **HIV**-1(LAI) envelope region; three of these **CTL** clones also recognized targets expressing envelope from a similar viral subtype, **HIV**-1(MN). The epitope specificity of CD4+ clone 9G8, recognizing both **HIV**-1(LAI) and **HIV**-1(MN) envelope, was within the 571-590 amino acid envelope region. Sequence analysis of the first infectious autologous strain revealed two amino acid mutations within this region. The 9G8 **CTL** clone induced by immunization failed to recognize targets expressing the corresponding **CTL** epitope from the infecting virus. Moreover, a peptide based on the epitope sequence of the infecting isolate antagonized the **vaccine**-induced **CTL** clone such that the **CTL** clone was no longer able to recognize the **vaccine** strain or **HIV**-1(MN) epitope. These findings suggest a potentially novel mechanism associated with **vaccine** failure whereby the infecting virus may not only **escape** from **CTL** activity, but also alter the ability of **CTL** to

recognize other variants in an individual.

L33 ANSWER 68 OF 78 MEDLINE on STN
97141290. PubMed ID: 8987634. Evaluation of hepatitis C virus protein epitopes for **vaccine** development. Koshy R; Inchauspe G. (Department of Virology, Royal Postgraduate Medical School, Hammersmith Hospital, London, UK.. rkoshy@rpms.ac.uk) . Trends in biotechnology, (1996 Oct) 14 (10) 364-9. Ref: 40. Journal code: 8310903. ISSN: 0167-7799. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Infection with hepatitis C virus (HCV) leads to viral persistence and chronic disease in a very high proportion of cases, despite a broad immunological response to viral proteins. These responses may thwarted by the high rate of mutation, which leads to the generation of **'escape'** variants of HCV that persist as a quasi-species in infected individuals. The specificity of the immuno response of infected patients suggests that responses directed at certain viral epitopes may be associated with less aggressive disease and, possibly, good interferon response and virus clearance. The identification of such epitopes may hold the key for future development both of prophylactic and **therapeutic vaccines**.

L33 ANSWER 69 OF 78 MEDLINE on STN
95353766. PubMed ID: 7627623. Mechanism of **HIV** persistence: implications for **vaccines** and **therapy**. Bremermann H J. (Department of Molecular and Cell Biology, University of California, Berkeley, USA.) Journal of acquired immune deficiency syndromes and human retrovirology : official publication of the International Retrovirology Association, (1995 Aug 15) 9 (5) 459-83. Ref: 67. Journal code: 9501482. ISSN: 1077-9450. Pub. country: United States. Language: English.

AB Periodic infusion of autologous **HIV**-antigen presenting cells (APCs), that stimulate the cytotoxic (**CTL**) response, while being incapable of producing virus, should lower viral burden and boost CD4+ count in **HIV**-seropositive individuals. Viral burden reasserts itself after antiviral **therapy** ceases or is interrupted for long. **Therapy**, therefore, would have to continue for life. These are predictions from a computer model of **HIV**-immune kinetics. The model equations describe the interactive kinetics of viral burden, CD4+ cell decline, neutralization of free virus by antibodies, infection of cells, and killing of infected cells by **CTL**. The computed trajectories of the kinetic equations reproduce the typical course of an **HIV** infection and the model yields several predictions that are not intuitively obvious, among them: (a) Persistence of **HIV** infection (failure of the immune system to clear infection) is an intrinsic property of the kinetics of the **HIV**-immune interaction. (b) The chronic state of infection is inherently stable, which means that the infection rebounds to the determined steady state, whenever antiviral **therapy** stops. (c) **CTL** is chronically activated, and the level correlates inversely with the avidity of neutralizing antibodies. (d) APCs have to be infused at a rate such as to boost and maintain the **CTL** response above the chronic level. Other **therapies** include **CTL** stimulation, via the macrophage route, by erythrocytes, into which MHC binding **HIV-CTL** epitope polypeptide fragments have been inserted; passive immunization, virion-trapping by CD4 analogs or CD4 expressing erythrocytes; and combination **therapies** with AZT, IL-2. These are also analyzed. Concerning **HIV** etiology, the model assumes that cells other than CD4+ cells (such as macrophages/monocytes) become infected, and contribute to the viral burden, and that infectible cells remain available even as CD4+ cells become exhausted. The model further assumes that CD4+ cells decline not only through direct killing by **HIV** and **CTL**, but by dysregulation and excess apoptosis caused by the presence of virus. The model predicts that persistence of **HIV** infection does not depend upon latently infected cells or **escape** mutants, as has been suggested.(ABSTRACT TRUNCATED AT 400 WORDS)

L33 ANSWER 70 OF 78 MEDLINE on STN
95336690. PubMed ID: 7612234. Principles for adoptive T cell **therapy** of human viral diseases. Riddell S R; Greenberg P D. (Program in Immunology, Fred Hutchinson Cancer Research Center, Seattle, Washington 98104, USA.)

Annual review of immunology, (1995) 13 545-86. Ref: 249. Journal code: 8309206. ISSN: 0732-0582. Pub. country: United States. Language: English.

AB The development of successful adoptive immunotherapy for human virus infections is predicated on an understanding of the effector cells and mechanisms essential for providing the host with a protective response to acute infection and the requirements for long-term in vivo survival of transferred cells that will be necessary to provide memory responses to persistent and latent viral infections. In this review, we discuss the results of recent studies examining the effector mechanisms mediated by virus-specific alpha beta + T cells and the strategies viruses have evolved to evade recognition by such T cells and/or to interfere with the expression of T cell effector functions. The **evasion** strategies employed by individual viruses can render T cell subsets or T cells of particular specificities less effective in eliminating virally infected cells, and consequently they are less desirable choices for use in adoptive **therapy**. Insights derived from described studies of the pathogenesis and immunobiology of virus infections have resulted in the development of clinical adoptive immunotherapy studies for infections with CMV, EBV, and **HIV**. Although the results from such studies are preliminary, the principle that virus-specific T cells can be successfully transferred and can mediate **therapeutic** efficacy in humans has already been affirmed. The use of recently developed methods, such as retroviral-mediated gene transfer, to genetically modify antigen-specific T cell clones provides a novel approach to overcome limitations and improve on the safety and efficacy observed in these initial studies, suggesting that more widespread use of adoptive transfer of specific T cells as a **therapeutic** regimen should be feasible in the near future.

L33 ANSWER 71 OF 78 MEDLINE on STN

95312083. PubMed ID: 7791879. Antigenic oscillations and shifting immunodominance in **HIV**-1 infections. Nowak M A; May R M; Phillips R E; Rowland-Jones S; Lalloo D G; McAdam S; Klenerman P; Koppe B; Sigmund K; Bangham C R; +. (Department of Zoology, University of Oxford, UK.) Nature, (1995 Jun 15) 375 (6532) 606-11. Journal code: 0410462. ISSN: 0028-0836. Pub. country: ENGLAND: United Kingdom. Language: English.

AB A typical protein antigen contains several epitopes that can be recognized by **cytotoxic T lymphocytes** (**CTL**), but in a characteristic antiviral immune response in vivo, **CTL** recognize only a small number of these potential epitopes, sometimes only one, this phenomenon is known as immunodominance. Antigenic variation within **CTL** epitopes has been demonstrated for the **human immunodeficiency virus HIV**-1 (ref. 11) and other viruses and such 'antigenic **escape**' may be responsible for viral persistence. Here we develop a new mathematical model that deals with the interaction between **CTL** and multiple epitopes of a genetically variable pathogen, and show that the nonlinear competition among **CTL** responses against different epitopes can explain immunodominance. This model suggests that an antigenically homogeneous pathogen population tends to induce a dominant response against a single epitope, whereas a heterogeneous pathogen population can stimulate complicated fluctuating responses against multiple epitopes. Antigenic variation in the immunodominant epitope can shift responses to weaker epitopes and thereby reduce immunological control of the pathogen population. These ideas are consistent with detailed longitudinal studies of **CTL** responses in **HIV**-1 infected patients. For **vaccine** design, the model suggests that the major response should be directed against conserved epitopes even if they are subdominant.

L33 ANSWER 72 OF 78 MEDLINE on STN

95194699. PubMed ID: 7888194. Comparative biology and pathogenesis of AIDS and hepatitis B viruses: related but different. Hilleman M R. (Merck Institute for Therapeutic Research, Merck Research Laboratories, West Point, Pennsylvania 19486.) AIDS research and human retroviruses, (1994 Nov) 10 (11) 1409-19. Ref: 80. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB AIDS (**HIV**) and hepatitis B viruses are remarkably similar in their sharing of reverse transcription, in their ancestral origins and common

genetic elements, and in their modes of transmission. Both are hypermutable and exist as quasispecies due primarily to errors in reverse transcription, though there is severe restriction in the replicative competence of most hepatitis B mutants. They differ in the lack of an integrase in hepatitis B virus and in their pathogenesis in the infected host. **HIV** survives mainly by antigenic variability, immune **evasion,** and impairment of immune function though viral regulatory control elements seek to restrict fatal damage to the host. Hepatitis B virus survives primarily by mutation of e antigen/core genes that directly obviates **cytotoxic T cell** destruction of infected liver cells, or indirectly limits destruction of infected cells through induction of anergy in the **cytotoxic T cell** response. Most persons infected with hepatitis B virus recover completely while recovery from **HIV** infection is rare if ever. Hepatitis B is highly **preventable** by **vaccine** while **HIV** **vaccine** is still seeking a meaningful immunoprophylactic target. AIDS and hepatitis B represent an extreme example, among the viruses of man, in their close similarities but distinct differences. In depth details and perspectives are presented in this review.

L33 ANSWER 73 OF 78 MEDLINE on STN
95015873. PubMed ID: 7523505. A region of the third variable loop of **HIV**-1 gp120 is recognized by HLA-B7-restricted CTLs from two acute seroconversion patients. Safrit J T; Lee A Y; Andrews C A; Koup R A. (Aaron Diamond AIDS Research Center and the Department of Medicine and Microbiology, New York University, School of Medicine, New York 10016.) Journal of immunology (Baltimore, Md. : 1950), (1994 Oct 15) 153 (8) 3822-30. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB **HIV**-1 envelope-specific **CTL** clones were isolated from the peripheral blood of two patients from within weeks of seroconversion. These clones were **CD8**+ and restricted by the HLA-B7 molecule. The minimum epitope recognized by the clones was determined to be the 30-amino acid (aa) sequence RPNNNTRKSI within the third variable (V3) loop of the envelope glycoprotein gp120. The aa sequence of this epitope is consistent with the motif found in naturally processed peptides eluted from HLA-B7 molecules. This region of the V3 loop is reasonably well conserved among clade B and some nonclade B isolates of **HIV**-1, especially at the anchor residues that determine binding to the HLA-B7 molecule. Using peptides based upon virus sequences present within each patient, we determined that autologous viruses were recognized by the clones, and we detected no **escape** variants from the initial clonal response during the acute phase of infection. Interestingly, a serine to arginine change at position 9 of the epitope abrogated clone recognition in one of the patients. This aa change is one factor that has been associated with a change from a nonsyncytium-inducing to a syncytium-inducing phenotype of **HIV**-1, raising the possibility that in HLA-B7-expressing patients, **escape** from this clonal **CTL** response and a change in viral phenotype may be linked. This study demonstrates that human **CTL** can be generated against sequences within the third variable loop of **HIV**-1 gp120. Because multiple **vaccine** strategies are based upon the V3 loop of **HIV**-1 gp120, this defined epitope can be exploited in determining the ability of certain **vaccines** to stimulate a **CTL** response in a select population of individuals.

L33 ANSWER 74 OF 78 MEDLINE on STN
94238428. PubMed ID: 8182510. The rationale for immunotherapy in **HIV**-1 infection. Walker B D. (Harvard Medical School, Infectious Disease Unit, Massachusetts General Hospital, Boston 02114.) Journal of acquired immune deficiency syndromes, (1994) 7 Suppl 1 S6-13. Ref: 53. Journal code: 8812597. ISSN: 0894-9255. Pub. country: United States. Language: English.

AB **Human immunodeficiency virus** type 1 (**HIV**-1) infection causes progressive and ultimately profound immunosuppression. Initially, however, infection is associated with vigorous virus-specific immune responses, including both neutralizing antibodies and **cytotoxic T lymphocytes** (CTLs). Although the host immune response is ultimately unable to eliminate the virus, experimental data suggest that these immune

responses help to inhibit virus replication during the prolonged asymptomatic phase of illness. A number of mechanisms have been proposed to contribute to viral persistence in infected persons, among them direct immunosuppressive effects of the virus; defects in antigen presentation; down-modulation of human leukocyte antigens (HLA); clonal deletion of existing immune responses; sequence variation leading to immune **escape**; and decreased T-helper cell function. The rationale supporting the use of **vaccine therapy** in **HIV**-1 infection is based on the hypothesis that viral persistence is due to an inadequate immune response generated by natural infection and that the immune system can be induced to generate more effective immunoregulatory responses by **vaccination**. Potential mechanisms by which this might occur include enhanced clearance of circulating virus, enhanced recognition of virus variants, enhanced presentation of viral antigens to the immune system, and increased regional T-cell help. A number of protocols evaluating **vaccine therapy** in **HIV**-1 infection are presently under way, the results of which should facilitate rational decisions regarding the use of this approach in **HIV**-1-infected persons.

L33 ANSWER 75 OF 78 MEDLINE on STN

94187120. PubMed ID: 7511178. An epitope in the V1 domain of the simian immunodeficiency virus (SIV) gp120 protein is recognized by **CD8+ cytotoxic T lymphocytes** from an SIV-infected rhesus macaque. Erickson A L; Walker C M. (Chiron Corporation, Emeryville, California 94608.) Journal of virology, (1994 Apr) 68 (4) 2756-9. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB **Cytotoxic T-lymphocyte** (**CTL**) responses against the external envelope glycoprotein (gp120) of the simian immunodeficiency virus (SIV) were studied in a rhesus macaque infected with SIVmac/239. **CD8**+ T cells enriched from concanavalin A-stimulated peripheral blood mononuclear cells lysed autologous target cells infected with recombinant **vaccinia** virus vectors expressing the SIVmac/239 or SIVsm/H4 envelope protein, which share approximately 80% identity in amino acid sequence. A **CD8+ CTL** line derived by limiting dilution culture of the concanavalin A-stimulated lymphocytes was also specific for the envelope proteins of both SIV isolates. Mapping studies revealed that this cell line recognized an epitope between amino acids 113 and 121 (CNKSETDRW) in the V1 domain of gp120. Amino acid substitutions are observed at positions 116 and 120 among viruses of the SIVsm/mac/**human immunodeficiency virus** type 2 group, and thus synthetic peptides representing these variants were tested for the ability to sensitize target cells for lysis by the **CTL** line. Autologous target cells sensitized with a synthetic peptide representing the SIVmac/239 sequence were efficiently killed. In contrast, recognition of target cells was reduced or abolished when peptides representing the amino acid substitutions at position 116 or 120 of other SIVmac, SIVsm, SIVmne, or SIVstm strains were tested. Further studies of **CTL** responses against this epitope could provide insights into mechanisms of variability within the gp120 V1 domain and its importance in **evasion** of immunity in infected or **vaccinated** monkeys.

L33 ANSWER 76 OF 78 MEDLINE on STN

93331696. PubMed ID: 8393233. Virus-induced immunosuppression. 1. Age at infection relates to a selective or generalized defect. Tishon A; Borrow P; Evans C; Oldstone M B. (Department of Neuropharmacology, Scripps Research Institute, La Jolla, California 92037.) Virology, (1993 Aug) 195 (2) 397-405. Journal code: 0110674. ISSN: 0042-6822. Pub. country: United States. Language: English.

AB Viruses that persist must develop strategies to **escape** immunologic surveillance in order to survive. Investigation of lymphocytic choriomeningitis virus (LCMV)-induced persistence has indicated that this virus avoids immune clearance mainly by aborting the viral specific **cytotoxic T lymphocyte** (**CTL**) response, a response that is necessary for terminating viral infection. This study demonstrates that persistence established in immunologically immature newborns selectively depletes the LCMV-specific **CTL** response but does not hinder **CTL** responses to the RNA and DNA viruses influenza, **vaccinia**, or herpes

simplex. In contrast, persistence established in immunologically mature adults leads not to selective but rather to generalized immunosuppression during which **CTL** responses to LCMV, influenza, **vaccinia**, and herpes simplex viruses are all ablated or down-regulated. These results indicate that the state of maturity of the immune system at the time of virus-induced immunosuppression can result in two distinct phenotypes. These observations may account for the differing patterns of infection caused by hepatitis B virus or **human immunodeficiency virus** initiated in the neonatal period compared to that initiated in adulthood.

L33 ANSWER 77 OF 78 MEDLINE on STN
93046227. PubMed ID: 1423323. T cell immune response to cancer in humans and its relevance for immunodiagnosis and **therapy**. Oliver R T; Nouri A M. (Department of Medical Oncology, Royal London Hospital Medical College.) Cancer surveys, (1992) 13 173-204. Ref: 133. Journal code: 8218015. ISSN: 0261-2429. Pub. country: United States. Language: English.

AB Review of the relationship between the degree of immunosuppression and malignancy in patients on immunosuppressive drugs or immunosuppressed by **HIV** infection, postoperative blood transfusion or pregnancy provides the most convincing evidence of the importance of intact T cell immunity in resistance to cancer. Defective HLA class I and II antigen expression on tumours arising in non-immunosuppressed individuals and correlation of these changes with increased malignancy and diminished TIL provide the most convincing evidence that one factor necessary to ensure survival of most spontaneous tumours is mutation that enables tumour cells to **escape** rejection by **cytotoxic T cells**. These changes are less frequent in tumours in immunosuppressed patients, and preliminary data suggest that use of cytokine **therapy** is more successful in these tumours and the one in five spontaneous tumours demonstrating normal expression of HLA antigens and high levels of T cell infiltration. These observations suggest that future use of this **therapy** should be focused on these cases. All modalities of cancer **therapy** except hormone **therapy** (ie surgery, radiotherapy and chemotherapy) suppress immune responses. Defects of HLA antigen expression are less marked in early cancer. Combinations of immunotherapy with conventional treatment at presentation, including hormone **therapy** in view of data demonstrating regeneration of the thymus after castration, needs further investigation. Preliminary results from randomized trials involving nearly 300 individuals accidentally exposed to carcinogens demonstrated nearly 60% reduction of incidence of malignancy at 5 years in the arm receiving non-specific immunotherapy. If confirmed, such an approach might be more cost-effective as an approach for cancer **prevention** than organ specific cancer screening or **vaccination** against cancer associated viruses such as hepatitis B or papillomaviruses.

L33 ANSWER 78 OF 78 MEDLINE on STN
92202878. PubMed ID: 1372650. Identification of overlapping HLA class I-restricted **cytotoxic T cell** epitopes in a conserved region of the **human immunodeficiency virus** type 1 envelope glycoprotein: definition of minimum epitopes and analysis of the effects of sequence variation. Johnson R P; Trocha A; Buchanan T M; Walker B D. (Infectious Disease Unit, Massachusetts General Hospital, Boston 02114.) Journal of experimental medicine, (1992 Apr 1) 175 (4) 961-71. Journal code: 2985109R. ISSN: 0022-1007. Pub. country: United States. Language: English.

AB Although the immunologic basis of protective immunity in **human immunodeficiency virus** type 1 (**HIV**-1) infection has not yet been defined, virus-specific **cytotoxic T lymphocytes** (**CTL**) are likely to be an important host defense and may be a critical feature of an effective **vaccine**. These observations, along with the inclusion of the **HIV**-1 envelope in the majority of **vaccine** candidates presently in clinical trials, underscore the importance of the precise characterization of the cellular immune responses to this protein. Although humoral immune responses to the envelope protein have been extensively characterized, relatively little information is available regarding the envelope epitopes recognized by virus-specific **CTL** and the effects of sequence variation within these epitopes. Here we report the identification of two

overlapping **CTL** epitopes in a highly conserved region of the **HIV**-1 transmembrane envelope protein, gp41, using **CTL** clones derived from two seropositive subjects. An eight-amino acid peptide was defined as the minimum epitope recognized by HLA-B8-restricted **CTL** derived from one subject, and in a second subject, an overlapping nine-amino acid peptide was identified as the minimal epitope for HLA-B14-restricted **CTL** clones. Selected single amino acid substitutions representing those found in naturally occurring **HIV**-1 isolates resulted in partial to complete loss of recognition of these epitopes. These data indicate the presence of a highly conserved region in the **HIV**-1 envelope glycoprotein that is immunogenic for **CTL** responses. In addition, they suggest that natural sequence variation may lead to **escape** from immune detection by **HIV**-1-specific **CTL**. Since the region containing these epitopes has been previously shown to contain an immunodominant B cell epitope and also overlaps with a major histocompatibility complex class II T cell epitope recognized by CD4+ **CTL** from **HIV**-1 rgp160 **vaccine** recipients, it may be particularly important for **HIV**-1 **vaccine** development. Finally, the identification of minimal **CTL** epitopes presented by class I HLA molecules should facilitate the definition of allele-specific motifs.

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=> d his

     (FILE 'HOME' ENTERED AT 19:42:02 ON 01 APR 2004)

     FILE 'USPATFULL' ENTERED AT 19:42:32 ON 01 APR 2004
                E FRANCHINI GENOVEFFA/IN
L1            7 S E3
L2            0 S ZDENEK HEL/IN
                E ZDENEK HEL/IN
L3            0 S HEL ZDENEK/IN S HEL ZDENEK/IN
L4            0 S GENE SHEARER/IN
L5            1 S SHEARER GENE/IN
                E SHEARER GENE/IN
L6            7 S E4
                E NACSA JANOS/IN

     FILE 'MEDLINE' ENTERED AT 19:47:38 ON 01 APR 2004
                E FRANCHINI G/AU
L7          196 S E3 OR E4
L8           67 S L7 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L9           16 S L8 AND (MHC OR MAJOR HISTOCOMPATIBILITY OR CTL OR CYTOTOXIC T
L10           0 S HEL Z/AU S HEL Z/AU
                E SHEARER G M/AU
L11         358 S E3 OR E6 OR E7
L12         118 S L11 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L13          20 S L12 AND (MAJOR HISTOCOMPATIBILITY OR CTL OR CYTOTOXIC)
                E NACSA J/AU
L14          22 S E3 OR E4

     FILE 'WPIDS' ENTERED AT 20:01:20 ON 01 APR 2004
                E FRANCHINI G/IN
L15          18 S E3
L16          10 S L15 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
                E SHEARER G M/IN
L17          10 S E3
L18          15 S E3 OR E2
                E NACSA J/IN
L19           3 S E3

     FILE 'USPATFULL' ENTERED AT 20:09:31 ON 01 APR 2004
L20       31746 S (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L21       10927 S L20 AND (CTL OR CYTOTOXIC)
L22        1761 S L21 AND (HIV/CLM OR HUMAN IMMUNODEFICIENCY VIRUS/CLM)
L23         233 S L22 AND (CTL/CLM OR CYTOTOXIC/CLM)
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L24          [illegible] S L23 AND (VACCIN? OR IMMUNOGEN?)
L25          182 S L24 AND (PROTECT? OR PREVENT?)
L26           96 S L25 AND (DNA/CLM OR NUCLEIC ACID/CLM)
L27           33 S L26 AND AY<2000
L28            1 S US6656471/PN
L29            1 S US6319666/PN

     FILE 'MEDLINE' ENTERED AT 20:22:25 ON 01 APR 2004
L30       139974 S (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L31         5709 S L30 AND (CTL OR CYTOTOXIC T CELL? OR CYTOTOXIC T LYMPHOCYTE?
L32          176 S L31 AND (ESCAPE OR EVASION)
L33           78 S L32 AND (VACCIN? OR PREVENT? OR THERAP?)

=>
=> s l32 not l33
L34           98 L32 NOT L33

=> d l34,cbib,ab,1-98
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L34 ANSWER 1 OF 98 MEDLINE on STN

2004159528. PubMed ID: 15053338. **CD8**+ T-cells: function and response to **HIV** infection. Gulzar Naveed; Copeland Karen F T. (Ottawa Health Research Institute, Ottawa, Ontario, Canada.) Curr HIV Res, (2004 Jan) 2 (1) 23-37. Journal code: 101156990. ISSN: 1570-162X. Pub. country: Netherlands. Language: English.

AB **CD8**+ T-cells are a critical component of the cellular immune response and they play an important role in the control of viral infection. During **HIV** infection, **CD8**+ T-cells are able to recognize infected cells through an MHC-I dependent process and are able to lyse cells harboring viral infection by the secretion of perforin and granzymes. These **cytotoxic T-lymphocytes** (**CTL**) can also eliminate virally infected cells through the engagement of death-inducing ligands expressed by **CD8**+ T-cells with death receptors on the surface of the infected cell. In addition, **CD8**+ **CTL** secrete soluble factors such as beta-chemokines and the **CD8**+ antiviral factor (CAF) that suppress viral binding and transcription, respectively. In order for **HIV** to survive the pressures placed upon it by the immune system, the virus has adopted numerous strategies to evade the **CD8**+ T-cell response. The high mutation rate of **HIV** has allowed the virus to **escape** **CD8**+ T-cell recognition in addition to its ability to down-regulate surface MHC-I expression from infected cells. Also, by altering the pattern of cytokine production and engagement of cellular receptors, **HIV** disrupts proper **CD8**+ T-cell signaling. The resultant improper T-cell receptor (TcR) stimulation creates an anergic state in these cells. By affecting the function of CD4+ T-cells and antigen presenting cells that are required for proper **CD8**+ T-cell maturation, **HIV** is able to decrease the circulating pool of effector and memory **CD8**+ T-cells that are able to combat viral infection. The end result is the aberration of **CD8**+ T-cell function.

L34 ANSWER 2 OF 98 MEDLINE on STN

2004153040. PubMed ID: 15046259. The evolutionary adaptation of **HIV**-1 to specific immunity. da Silva Jack. (North Carolina Supercomputing Center, PO Box 12889, 3021 Cornwallis Road, Research Triangle Park, NC 27516, USA.. jdasilva@ncsc.org) . Curr HIV Res, (2003 Jul) 1 (3) 363-71. Journal code: 101156990. ISSN: 1570-162X. Pub. country: Netherlands. Language: English.

AB Recent evidence of the evolutionary adaptation of **HIV**-1 to the specific immune system is reviewed. Longitudinal studies of patients show that a neutralizing antibody (NAb) response specific to autologous virus is detectable within 1-2 months of infection and that viral variants resistant to neutralization arise and spread in the viral population within the subsequent three months, and that this general pattern is repeated. There is strong evidence that amino acid replacements in gp120 glycan-binding motifs affect viral sensitivity to neutralization and are selected by NAbs. Longitudinal studies of humans have also provided good evidence of amino acid replacements in **cytotoxic T lymphocyte**

(CTL) epitopes that allow the virus to **escape** detection by CTLs. But, the clearest evidence of adaptation to **CTL** surveillance at the molecular level comes from experiments with SIV-infected rhesus macaques. These show unequivocally that amino acid replacements in **CTL** epitopes are the result of positive selection and that these **escape** mutants have a lower class I major histocompatibility complex (MHC) binding affinity or are less likely to be recognized by CTLs than non-**escape** variants. To improve our ability to predict **HIV**'s evolutionary responses to selection by the specific immune system it is suggested that future work focus on the details of the adaptive response to antibody surveillance, the temporal dynamics of specific immune responses, the relative importance of antibody and **CTL** selection, and the effects of superinfection, viral recombination, and viral protein functional constraints on immune **escape**.

L34 ANSWER 3 OF 98 MEDLINE on STN
2004101208. PubMed ID: 14770175. **HIV** evolution: **CTL escape** mutation and reversion after transmission. Leslie A J; Pfafferott K J; Chetty P; Draenert R; Addo M M; Feeney M; Tang Y; Holmes E C; Allen T; Prado J G; Altfeld M; Brander C; Dixon C; Ramduth D; Jeena P; Thomas S A; John A St; Roach T A; Kupfer B; Luzzi G; Edwards A; Taylor G; Lyall H; Tudor-Williams G; Novelli V; Martinez-Picado J; Kiepiela P; Walker B D; Goulder P J R. ([1] Department of Pediatrics, Fuffield Department of Medicine, Peter Medawar Building for Pathogen Research, University of Oxford, Oxford OX1 3SY, UK. [2] These authors contributed equally to this work.) Nature medicine, (2004 Mar) 10 (3) 282-9. Journal code: 9502015. ISSN: 1078-8956. Pub. country: United States. Language: English.

AB Within-patient **HIV** evolution reflects the strong selection pressure driving viral **escape** from **cytotoxic T-lymphocyte** (**CTL**) recognition. Whether this intrapatient accumulation of **escape** mutations translates into **HIV** evolution at the population level has not been evaluated. We studied over 300 patients drawn from the B- and C-clade epidemics, focusing on human leukocyte antigen (HLA) alleles HLA-B57 and HLA-B5801, which are associated with long-term **HIV** control and are therefore likely to exert strong selection pressure on the virus. The **CTL** response dominating acute infection in HLA-B57/5801-positive subjects drove positive selection of an **escape** mutation that reverted to wild-type after transmission to HLA-B57/5801-negative individuals. A second **escape** mutation within the epitope, by contrast, was maintained after transmission. These data show that the process of accumulation of **escape** mutations within **HIV** is not inevitable. Complex epitope- and residue-specific selection forces, including **CTL**-mediated positive selection pressure and virus-mediated purifying selection, operate in tandem to shape **HIV** evolution at the population level.

L34 ANSWER 4 OF 98 MEDLINE on STN
2003544530. PubMed ID: 14610167. Identification of sequential viral **escape** mutants associated with altered T-cell responses in a **human immunodeficiency virus** type 1-infected individual. Geels Mark J; Cornelissen Marion; Schuitemaker Hanneke; Anderson Kiersten; Kwa David; Maas Jolanda; Dekker John T; Baan Elly; Zorgdrager Fokla; van den Burg Remco; van Beelen Martijn; Lukashov Vladimir V; Fu Tong-Ming; Paxton William A; van der Hoek Lia; Dubey Sheri A; Shiver John W; Goudsmit Jaap. (Department of Human Retrovirology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands.) Journal of virology, (2003 Dec) 77 (23) 12430-40. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Control of viremia in natural **human immunodeficiency virus** type 1 (**HIV**-1) infection in humans is associated with a virus-specific T-cell response. However, still much is unknown with regard to the extent of **CD8**(+) **cytotoxic T-lymphocyte** (**CTL**) responses required to successfully control **HIV**-1 infection and to what extent **CTL** epitope **escape** can account for rises in viral load and ultimate progression to disease. In this study, we chose to monitor through full-length genome sequence of replication-competent biological clones the modifications that occurred within predicted **CTL** epitopes and to identify whether the alterations resulted in epitope **escape** from **CTL** recognition. From an

extensive analysis of 59 biological HIV-1 clones generated over a period of 4 years from a single individual in whom the viral load was observed to rise, we identified the locations in the genome of five **CD8**(+) **CTL** epitopes. Fixed mutations were identified within the p17, gp120, gp41, Nef, and reverse transcriptase genes. Using a gamma interferon ELIspot assay, we identified for four of the five epitopes with fixed mutations a complete loss of T-cell reactivity against the wild-type epitope and a partial loss of reactivity against the mutant epitope. These results demonstrate the sequential accumulation of **CTL escape** in a patient during disease progression, indicating that multiple combinations of T-cell epitopes are required to control viremia.

L34 ANSWER 5 OF 98 MEDLINE on STN
2003544514. PubMed ID: 14607940. Epitope **escape** mutation and decay of **human immunodeficiency virus** type 1-specific **CTL** responses. Jamieson Beth D; Yang Otto O; Hultin Lance; Hausner Mary Ann; Hultin Patricia; Matud Jose; Kunstman Kevin; Killian Scott; Altman John; Kommander Kristina; Korber Bette; Giorgi Janis; Wolinsky Steven. (Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA 90095, USA.. jamieson@mednet.ucla.edu) . Journal of immunology (Baltimore, Md. : 1950), (2003 Nov 15) 171 (10) 5372-9. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB To investigate possible mechanisms behind **HIV**-1 **escape** from **CTL**, we performed detailed longitudinal analysis of Gag (SLYNTVATL)- and RT (ILKEPVHGV)-specific **CTL** responses and plasma epitope sequences in five individuals. Among those with **CTL** against consensus epitope sequences, epitope mutations developed over several years, invariably followed by decay of the **CTL** targeting the consensus epitopes. The maturation state of the **CTL** varied among individuals and appeared to affect the rate of epitope mutation and **CTL** decay, despite similar IFN-gamma production. **Escape** mutations were oligoclonal, suggesting fitness constraints. The timing of **escape** indicated that the net selective advantage of **escape** mutants was slight, further underscoring the importance of understanding factors determining selective pressure and viral fitness in vivo. Our data show surprisingly consistent decay of **CTL** responses after epitope **escape** mutation and provide insight into potential mechanisms for both immune failure and shifting **CTL** specificities.

L34 ANSWER 6 OF 98 MEDLINE on STN
2003532441. PubMed ID: 14610180. Simian-**human immunodeficiency virus escape** from **cytotoxic T-lymphocyte** recognition at a structurally constrained epitope. Peyerl Fred W; Barouch Dan H; Yeh Wendy W; Bazick Heidi S; Kunstman Jennifer; Kunstman Kevin J; Wolinsky Steven M; Letvin Norman L. (Division of Viral Pathogenesis, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts 02215, USA.) Journal of virology, (2003 Dec) 77 (23) 12572-8. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Virus-specific **cytotoxic T lymphocytes** (**CTL**) exert intense selection pressure on replicating simian immunodeficiency virus (SIV) and **human immunodeficiency virus** type 1 (**HIV**-1) in infected individuals. The immunodominant Mamu-A(*)01-restricted Gag p11C, C-M epitope is highly conserved among all sequenced isolates of SIV and therefore likely is structurally constrained. The strategies used by virus isolates to mutate away from an immunodominant epitope-specific **CTL** response are not well defined. Here we demonstrate that the emergence of a position 2 p11C, C-M epitope substitution (T47I) in a simian-**human immunodeficiency virus** (SHIV) strain 89.6P-infected Mamu-A(*)01(+) monkey is temporally correlated with the emergence of a flanking isoleucine-to-valine substitution at position 71 (I71V) of the capsid protein. An analysis of the SIV and **HIV**-2 sequences from the Los Alamos **HIV** Sequence Database revealed a significant association between any position 2 p11C, C-M epitope mutation and the I71V mutation. The T47I mutation alone is associated with significant decreases in viral protein expression, infectivity, and replication, and these deficiencies are restored to wild-type levels with the introduction of the flanking I71V mutation. Together, these data suggest that a compensatory mutation is

selected for in SHIV strain 89.6P to facilitate the **escape** of that virus from **CTL** recognition of the dominant p11C, C-M epitope.

L34 ANSWER 7 OF 98 MEDLINE on STN
2003517018. PubMed ID: 12947089. An in vivo replication-important function in the second coding exon of Tat is constrained against mutation despite **cytotoxic T lymphocyte** selection. Smith Stephen M; Pentlicky Sara; Klase Zachary; Singh Mahender; Neuveut Christine; Lu Chun-yi; Reitz Marvin S Jr; Yarchoan Robert; Marx Preston A; Jeang Kuan-Teh. (Saint Michael's Medical Center, Newark, New Jersey 07102, USA.. stephens@cathedralhealth.org) . Journal of biological chemistry, (2003 Nov 7) 278 (45) 44816-25. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB Human and simian immunodeficiency virus (**HIV**/SIV) Tat proteins are specified by two coding exons. Tat functions in the transcription of primate lentiviruses. A plethora of in vitro data currently suggests that the second coding exon of Tat is largely devoid of function. However, whether the second exon of Tat contributes functionally to viral pathogenesis in vivo remains unknown. To address this question directly, we compared infection of rhesus macaques with an SIV, engineered to express only the first coding exon of Tat (SIVtat1ex), to counterpart infection with wild-type SIVmac239 virus, which expresses the full 2-exon Tat. This comparison showed that the second coding exon of Tat contributes to chronic SIV replication in vivo. Interestingly, in macaques, we observed a **cytotoxic T lymphocytes** (**CTL**) response to the second coding exon of Tat, which appears to durably control SIV replication. When SIV mutated in an attempt to **escape** this second Tat-exon-**CTL**, the resulting virus was less replicatively fit and failed to populate the host in vivo. Our study provides the first evidence that the second coding exon in Tat embodies an important function for in vivo replication. We suggest the second coding exon of Tat as an example of a functionally constrained "epitope" whose elicited **CTL** response cannot be escaped by virus mutation without producing a virus that replicates poorly in vivo.

L34 ANSWER 8 OF 98 MEDLINE on STN
2003437381. PubMed ID: 13678464. An **HIV** type 1 subtype B founder effect in Korea: gp160 signature patterns infer circulation of **CTL-escape** strains at the population level. Daniels Rod S; Kang Chun; Patel Dina; Xiang Zheng; Douglas Nigel W; Zheng Natalie N; Cho Hae-Wol; Lee Joo-Shil. (Virology Division, National Institute for Medical Research, The Ridgeway, Mill Hill, London NW7 1AA, UK.. rdaniel@nimr.mrc.ac.uk) . AIDS research and human retroviruses, (2003 Aug) 19 (8) 631-41. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB **HIV**-1 subtype B predominates in the Republic of Korea. Phylogenetic analyses of sequences for complete nef genes and env gene fragments encoding the V3 loop have identified a major monophyletic Korean subclade that is distinct from Western subtype B sequences in the Los Alamos **HIV** Sequence Database. This was investigated further by sequence analysis of complete env genes recovered from the DNA of peripheral blood mononuclear cells for matched groups of Koreans, four patients per group, previously assigned as being infected with either Korean or Western strains. The phylogenetic classifications were confirmed and analysis of the translation products identified 32 amino acid signature pattern differences, dispersed throughout gp160, which differentiate the two subclades. Twenty-three of these positions map to epitopes recognized by HLA-I-restricted **cytotoxic T-lymphocytes** (**CTL**) as catalogued in the Los Alamos **HIV** Immunology Database. The remaining nine map at or close to sites predicted to be targets for immunoproteasomes that are involved in producing peptides that bind to MHC Class I. These results suggest that a founder effect in the Korean population is based on the spread of **CTL-escape**/host-adapted **HIV**-1 strains.

L34 ANSWER 9 OF 98 MEDLINE on STN
2003364775. PubMed ID: 12885919. Major histocompatibility complex class I alleles associated with slow simian immunodeficiency virus disease

progression bind epitopes recognized by dominant acute phase **cytotoxic-T-lymphocyte** responses. O'Connor David H; Mothe Bianca R; Weinfurter Jason T; Fuenger Sarah; Rehrauer William M; Jing Peicheng; Rudersdorf Richard R; Liebl Max E; Krebs Kendall; Vasquez Joshua; Dodds Elizabeth; Loffredo John; Martin Sarah; McDermott Adrian B; Allen Todd M; Wang Chenxi; Doxiadis G G; Montefiori David C; Hughes Austin; Burton Dennis R; Allison David B; Wolinsky Steven M; Bontrop Ronald; Picker Louis J; Watkins David I. (Wisconsin Regional Primate Research Center and Department of Pathology and Laboratory Medicine, Madison, Wisconsin, USA.) Journal of virology, (2003 Aug) 77 (16) 9029-40. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Certain major histocompatibility complex class I (MHC-I) alleles are associated with delayed disease progression in individuals infected with **human immunodeficiency virus** (**HIV**) and in macaques infected with simian immunodeficiency virus (SIV). However, little is known about the influence of these MHC alleles on acute-phase cellular immune responses. Here we follow 51 animals infected with SIV(mac)239 and demonstrate a dramatic association between Mamu-A*01 and -B*17 expression and slowed disease progression. We show that the dominant acute-phase **cytotoxic T lymphocyte** (**CTL**) responses in animals expressing these alleles are largely directed against two epitopes restricted by Mamu-A*01 and one epitope restricted by Mamu-B*17. One Mamu-A*01-restricted response (Tat(28-35)SL8) and the Mamu-B*17-restricted response (Nef(165-173)IW9) typically select for viral **escape** variants in early SIV(mac)239 infection. Interestingly, animals expressing Mamu-A*1 and -B*17 have less variation in the Tat(28-35)SL8 epitope during chronic infection than animals that express only Mamu-A*01. Our results show that MHC-I alleles that are associated with slow progression to AIDS bind epitopes recognized by dominant **CTL** responses during acute infection and underscore the importance of understanding **CTL** responses during primary **HIV** infection.

L34 ANSWER 10 OF 98 MEDLINE on STN

2003258250. PubMed ID: 12768008. The differential ability of HLA B*5701+ long-term nonprogressors and progressors to restrict **human immunodeficiency virus** replication is not caused by loss of recognition of autologous viral gag sequences. Migueles Stephen A; Laborico Alisha C; Imamichi Hiromi; Shupert W Lesley; Royce Cassandra; McLaughlin Mary; Ehler Linda; Metcalf Julia; Liu Shuying; Hallahan Claire W; Connors Mark. (Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20892, USA.) Journal of virology, (2003 Jun) 77 (12) 6889-98. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Although the HLA B(*)5701 class I allele is highly overrepresented among **human immunodeficiency virus** (**HIV**)-infected long-term nonprogressors (LTNPs), it is also present at the expected frequency (11%) in patients with progressive **HIV** infection. Whether B57(+) progressors lack restriction of viral replication because of **escape** from recognition of highly immunodominant B57-restricted gag epitopes by **CD8**(+) T cells remains unknown. In this report, we investigate the association between restriction of virus replication and recognition of autologous virus sequences in 27 B(*)57(+) patients (10 LTNPs and 17 progressors). Amplification and direct sequencing of single molecules of viral cDNA or proviral DNA revealed low frequencies of genetic variations in these regions of gag. Furthermore, **CD8**(+) T-cell recognition of autologous viral variants was preserved in most cases. In two patients, responses to autologous viral variants were not demonstrable at one epitope. By using a novel technique to isolate primary CD4(+) T cells expressing autologous viral gene products, it was found that 1 to 13% of **CD8**(+) T cells were able to respond to these cells by gamma interferon production. In conclusion, **escape**-conferring mutations occur infrequently within immunodominant B57-restricted gag epitopes and are not the primary mechanism of virus **evasion** from immune control in B(*)5701(+) **HIV**-infected patients. Qualitative features of the virus-specific **CD8**(+) T-cell response not measured by current assays remain the most likely determinants of the differential abilities of HLA B(*)5701(+) LTNPs

and progressors to restrict virus replication.

L34 ANSWER 11 OF 98 MEDLINE on STN
2003234003. PubMed ID: 12743169. Determinant of **HIV**-1 mutational **escape** from **cytotoxic T lymphocytes**. Yang Otto O; Sarkis Phuong Thi Nguyen; Ali Ayub; Harlow Jason D; Brander Christian; Kalams Spyros A; Walker Bruce D. (Division of Infectious Diseases, 37-121 CHS, UCLA Medical Center, 10833 LeConte Ave., Los Angeles, CA 90095, USA.. oyang@mednet.ucla.edu) . Journal of experimental medicine, (2003 May 19) 197 (10) 1365-75. Journal code: 2985109R. ISSN: 0022-1007. Pub. country: United States. Language: English.

AB **CD8+** class I-restricted **cytotoxic T lymphocytes** (CTLs) usually incompletely suppress **HIV**-1 in vivo, and while analogous partial suppression induces antiretroviral drug-resistance mutations, epitope **escape** mutations are inconsistently observed. However, **escape** mutation depends on the net balance of selective pressure and mutational fitness costs, which are poorly understood and difficult to study in vivo. Here we used a controlled in vitro system to evaluate the ability of **HIV**-1 to **escape** from **CTL** clones, finding that virus replicating under selective pressure rapidly can develop phenotypic resistance associated with genotypic changes. **Escape** varied between clones recognizing the same Gag epitope or different Gag and RT epitopes, indicating the influence of the T cell receptor on pressure and fitness costs. Gag and RT **escape** mutations were monoclonal intra-epitope substitutions, indicating limitation by fitness constraints in structural proteins. In contrast, **escape** from Nef-specific **CTL** was more rapid and consistent, marked by a polyclonal mixture of epitope point mutations and upstream frameshifts. We conclude that incomplete viral suppression by **CTL** can result in rapid emergence of immune **escape**, but the likelihood is strongly determined by factors influencing the fitness costs of the particular epitope targeted and the ability of responding **CTL** to recognize specific epitope variants.

L34 ANSWER 12 OF 98 MEDLINE on STN
2003084067. PubMed ID: 12594955. Rev activity determines sensitivity of **HIV**-1-infected primary T cells to **CTL** killing. Bobbitt Kevin R; Addo Marylyn M; Altfeld Marcus; Filzen Tracey; Onafuwa Adewunmi A; Walker Bruce D; Collins Kathleen L. (Department of Internal Medicine, The University of Michigan, Ann Arbor, MI 48109, USA.) Immunity, (2003 Feb) 18 (2) 289-99. Journal code: 9432918. ISSN: 1074-7613. Pub. country: United States. Language: English.

AB The **HIV** Nef protein is thought to promote **HIV** immune **evasion** by downmodulating MHC-I and protecting infected cells from **CTL** killing. In addition, we demonstrated that Rev, an **HIV** regulatory protein needed for expression of the **HIV** late genes, can influence **CTL** killing. When Rev activity level was reduced by virtue of amino acid alterations in the Rev protein sequence, infected cells were more resistant to anti-Gag and anti-Env **CTL** killing. A screen of primary viral isolates revealed that viruses derived from asymptomatic, infected people had lower Rev activity, lower Gag levels, and greater resistance to anti-Gag **CTL** killing. Thus, rev alleles with low activity may have a selective advantage in infected people with effective immune responses.

L34 ANSWER 13 OF 98 MEDLINE on STN
2002725271. PubMed ID: 12487820. **HIV** type 1 abrogates TAP-mediated transport of antigenic peptides presented by MHC class I. Transporter associated with antigen presentation. Kutsch O; Vey T; Kerkau T; Hunig T; Schimpl A. (Institute of Immunobiology and Virology, The Julius-Maximilians University, Wurzburg, Germany.. okutsch@uab.edu) . AIDS research and human retroviruses, (2002 Nov 20) 18 (17) 1319-25. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB Downregulation of MHC class I expression following **human immunodeficiency virus** 1 (**HIV**-1) infection is thought to play an important role in viral **escape** from immune recognition by **cytotoxic T-lymphocytes** (CTLs). Since exogenous addition of **HIV**-1-derived

peptides restores susceptibility of **HIV**-1-infected cells to **CTL**-mediated lysis, we tested whether endogenous peptide loading is impaired in these cells. Our results show that in **HIV**-1-infected cells the ability of the transporter associated with antigen presentation (TAP) to translocate antigenic peptides from the cytosol to the lumen of the ER for presentation on MHC class I molecules is abolished. These data suggest that interference with the supply of antigenic peptides to the MHC class I pathway provides an additional mechanism by which **HIV**-1 evades the **CTL**-mediated immune response.

L34 ANSWER 14 OF 98 MEDLINE on STN

2002636191. PubMed ID: 12356679. Trypanosoma cruzi down-regulates lipopolysaccharide-induced MHC class I on human dendritic cells and impairs antigen presentation to specific **CD8**(+) T lymphocytes. Van Overtvelt Laurence; Andrieu Muriel; Verhasselt Valerie; Connan Francine; Choppin Jeannine; Vercruysse Vincent; Goldman Michel; Hosmalin Anne; Vray Bernard. (Laboratoire d'Immunologie Experimentale (CP 615), Faculte de Medecine, Universite Libre de Bruxelles, 808 route de Lennik, 1070 Brussels, Belgium.) International immunology, (2002 Oct) 14 (10) 1135-44. Journal code: 8916182. ISSN: 0953-8178. Pub. country: England: United Kingdom. Language: English.

AB Trypanosoma cruzi, the etiological agent of Chagas' disease, may persist for many years in its mammalian host. This suggests **escape** from the immune response and particularly a suboptimal **CD8**(+) T cell response, since these cells are involved in infection control. In this report, we show that T. cruzi inhibits the lipopolysaccharide (LPS)-induced up-regulation of MHC class I molecules at the surface of human dendritic cells (DC). To further investigate the functional consequences of this inhibition, a trypomastigote surface antigen-derived peptide (TSA-1(514-522) peptide) was selected for its stable binding to HLA-A*0201 molecules and used to generate a primary T. cruzi-specific human **CD8**(+) T cell line in vitro. We observed that DC infected with T. cruzi or treated with T. cruzi-conditioned medium (TCM) had a weaker capacity to present this peptide to the specific **CD8**(+) T cell line as shown in an IFN-gamma ELISPOT assay. Interestingly, T. cruzi or TCM also reduced the antigen presentation capacity of DC to **CD8**(+) T cell lines specific for the influenza virus M(58-66) or **HIV** RT(476-484) epitopes. This dysfunction appears to be linked essentially to reduced MHC class I molecule expression since the stimulation of the RT(476-484) peptide-specific **CD8**(+) T cell line was shown to depend mainly on the MHC class I-TCR interaction and not on the co-stimulatory signals which, however, were also inhibited by T. cruzi. This impairment of DC function may represent a novel mechanism reducing in vivo the host's ability to combat efficiently T. cruzi infection.

L34 ANSWER 15 OF 98 MEDLINE on STN

2002416936. PubMed ID: 12163596. Clustering patterns of **cytotoxic T-lymphocyte** epitopes in **human immunodeficiency virus** type 1 (**HIV**-1) proteins reveal imprints of immune **evasion** on **HIV**-1 global variation. Yusim Karina; Kesmir Can; Gaschen Brian; Addo Marylyn M; Altfeld Marcus; Brunak Soren; Chigaev Alexandre; Detours Vincent; Korber Bette T. (Los Alamos National Laboratory, Los Alamos, New Mexico 87545. Santa Fe Institute, Santa Fe, New Mexico 87501, USA.) Journal of virology, (2002 Sep) 76 (17) 8757-68. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB The human **cytotoxic T-lymphocyte** (**CTL**) response to **human immunodeficiency virus** type 1 (**HIV**-1) has been intensely studied, and hundreds of **CTL** epitopes have been experimentally defined, published, and compiled in the **HIV** Molecular Immunology Database. Maps of **CTL** epitopes on **HIV**-1 protein sequences reveal that defined epitopes tend to cluster. Here we integrate the global sequence and immunology databases to systematically explore the relationship between **HIV**-1 amino acid sequences and **CTL** epitope distributions. **CTL** responses to five **HIV**-1 proteins, Gag p17, Gag p24, reverse transcriptase (RT), Env, and Nef, have been particularly well characterized in the literature to date. Through comparing **CTL** epitope

distributions in these five proteins to global protein sequence alignments, we identified distinct characteristics of **HIV** amino acid sequences that correlate with **CTL** epitope localization. First, experimentally defined **HIV CTL** epitopes are concentrated in relatively conserved regions. Second, the highly variable regions that lack epitopes bear cumulative evidence of past immune **escape** that may make them relatively refractive to CTLs: a paucity of predicted proteasome processing sites and an enrichment for amino acids that do not serve as C-terminal anchor residues. Finally, **CTL** epitopes are more highly concentrated in alpha-helical regions of proteins. Based on amino acid sequence characteristics, in a blinded fashion, we predicted regions in **HIV** regulatory and accessory proteins that would be likely to contain **CTL** epitopes; these predictions were then validated by comparison to new sets of experimentally defined epitopes in **HIV**-1 Rev, Tat, Vif, and Vpr.

L34 ANSWER 16 OF 98 MEDLINE on STN
2002394385. PubMed ID: 12144897. Update on Kaposi's sarcoma and other HHV8 associated diseases. Part 2: pathogenesis, Castleman's disease, and pleural effusion lymphoma. Hengge Ulrich R; Ruzicka Thomas; Tyring Stephen K; Stuschke Martin; Roggendorf Michael; Schwartz Robert A; Seeber Siegfried. (Department of Dermatology, Venerology, and Allergology, University of Essen, Germany.. ulrich.hengge@uni-essen.de) . Lancet infectious diseases, (2002 Jun) 2 (6) 344-52. Ref: 91. Journal code: 101130150. ISSN: 1473-3099. Pub. country: United States. Language: English.

AB The pathogenesis of Kaposi's sarcoma (KS) is better understood since the identification of the novel human herpesvirus 8 (HHV8), which can be found in all forms of KS. Viral oncogenesis and cytokine-induced growth, as well as some states of immunocompromise, contribute to its development. Several virally encoded genes--eg, bcl-2, interleukin 6, cyclin D, G-protein-coupled receptor, and interferon regulatory factor--provide key functions on cellular proliferation and survival. Growth promotion of KS is further stimulated by various proinflammatory cytokines and growth factors such as tumour necrosis factor a, interleukin 6, basic fibroblast growth factor, and vascular endothelial growth factor, resulting in a hyperplastic polyclonal lesion with predominant spindle cells derived from lymphoid endothelia. HHV8 has recently been discovered to **escape** HLA-class-I-restricted antigen presentation to **cytotoxic T lymphocytes** by increasing endocytosis of MHC class I chains from the cell surface, thus enabling latent infection and immune **escape** in primary and chronic infection. Multicentric Castleman's disease is a rare lymphoproliferative disorder of the plasma cell type, which has been reported in both **HIV**-seropositive and **HIV**-seronegative patients, and which frequently contains HHV8 DNA. Pleural effusion lymphoma, or body-cavity-based lymphoma, belongs to the group of non-Hodgkin B-cell lymphomas characterised by pleural, pericardial, or peritoneal lymphomatous effusions in the absence of a solid tumour mass. Pleural effusion lymphoma has an intermediate immunophenotype lacking B or T lymphocyte antigens and also belongs to the diseases associated with HHV8.

L34 ANSWER 17 OF 98 MEDLINE on STN
2002385256. PubMed ID: 12134033. Favorable and unfavorable HLA class I alleles and haplotypes in Zambians predominantly infected with clade C **human immunodeficiency virus** type 1. Tang Jianming; Tang Shenghui; Lobashevsky Elena; Myracle Angela D; Fideli Ulgen; Aldrovandi Grace; Allen Susan; Musonda Rosemary; Kaslow Richard A. (Department of Medicine, University of Alabama at Birmingham, Alabama 35294, USA. (Zambia-UAB HIV Research Project).) Journal of virology, (2002 Aug) 76 (16) 8276-84. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB The setpoint of viral RNA concentration (viral load [VL]) during chronic **human immunodeficiency virus** type 1 (**HIV**-1) infection reflects a virus-host equilibration closely related to **CD8**(+) **cytotoxic T-lymphocyte** (**CTL**) responses, which rely heavily on antigen presentation by the human major histocompatibility complex (MHC) (i.e., HLA) class I molecules. Differences in **HIV**-1 VL among 259 mostly clade

HIV Research Project (ZUHRP) were associated with several HLA class I alleles and haplotypes. In particular, general linear model analyses revealed lower log(10) VL among those with HLA allele B*57 (P = 0.002 [without correction]) previously implicated in favorable response and in those with HLA B*39 and A*30-Cw*03 (P = 0.002 to 0.016); the same analyses also demonstrated higher log(10) VL among individuals with A*02-Cw*16, A*23-B*14, and A*23-Cw*07 (P = 0.010 to 0.033). These HLA effects remained strong (P = 0.0002 to 0.075) after adjustment for age, gender, and duration of infection and persisted across three orders of VL categories (P = 0.001 to 0.084). In contrast, neither B*35 (n = 15) nor B*53 (n = 53) showed a clear disadvantage such as that reported elsewhere for these closely related alleles. Other HLA associations with unusually high (A*68, B*41, B*45, and Cw*16) or low (B*13, Cw*12, and Cw*18) VL were either unstable or reflected their tight linkage respecting disequilibria with other class I variants. The three consistently favorable HLA class I variants retained in multivariable models and in alternative analyses were present in 30.9% of subjects with the lowest (<10,000 copies per ml) and 3.1% of those with the highest (>100,000) VL. Clear differential distribution of HLA profiles according to level of viremia suggests important host genetic contribution to the pattern of immune control and **escape** during **HIV**-1 infection.

L34 ANSWER 18 OF 98 MEDLINE on STN
2002346015. PubMed ID: 12088683. Avoiding the kiss of death: how **HIV** and other chronic viruses survive. Lieberman Judy; Manjunath N; Shankar Premlata. (Center for Blood Research and Department of Pediatrics, Harvard Medical School, 800 Huntington Avenue, Boston, MA 02115, USA.. lieberman@cbr.med.harvard.edu) . Current opinion in immunology, (2002 Aug) 14 (4) 478-86. Ref: 80. Journal code: 8900118. ISSN: 0952-7915. Pub. country: England: United Kingdom. Language: English.

AB Virus-specific **CD8** T cells during chronic infection often exceed in numbers virus-replicating infected cells. Why then do antiviral **CD8** T cells not do a better job of controlling infection? Although viral strategies for immune **evasion** are well known, this review will focus on changes in the **CD8** T cell that interfere with cytolytic function. Most antiviral **CD8** T cells in chronic infection do not express perforin, a molecule that is required for cytolysis. IL-2 and other costimulatory signals can restore cytotoxicity that has been impaired, suggesting a role for CD4 T cell anergy. The chance to eradicate an infection by T cell mediated lysis is undermined after an infection becomes established, in part because the effector immune response is impaired in the setting of chronic antigen.

L34 ANSWER 19 OF 98 MEDLINE on STN
2002245562. PubMed ID: 11984594. Acute phase **cytotoxic T lymphocyte escape** is a hallmark of simian immunodeficiency virus infection. O'Connor David H; Allen Todd M; Vogel Thorsten U; Jing Peicheng; DeSouza Ivan P; Dodds Elizabeth; Dunphy Edward J; Melsaether Cheri; Mothe Bianca; Yamamoto Hiroshi; Horton Helen; Wilson Nancy; Hughes Austin L; Watkins David I. (Wisconsin Regional Primate Research Center and Department of Pathology and Laboratory Medicine, University of Wisconsin, Madison, Wisconsin, USA.) Nature medicine, (2002 May) 8 (5) 493-9. Journal code: 9502015. ISSN: 1078-8956. Pub. country: United States. Language: English.

AB **Cytotoxic T-lymphocyte** (**CTL**) responses peak coincident with the decline in acute **HIV** viremia. Despite two reports of **CTL**-resistant **HIV** variants emerging during acute infection, the contribution of acute **CTL escape** to **HIV** pathogenesis remains unclear. Difficulties inherent in studying acute **HIV** infection can be overcome by modeling virus-host interactions in SIV-infected rhesus macaques. We sequenced 21 complete simian immunodeficiency virus (SIV)mac239 genomes at four weeks post-infection to determine the extent of acute **CTL escape**. Here we show that viruses from 19 of 21 macaques escaped from CTLs during acute infection and that these **escape**-selecting CTLs were responsive to lower concentrations of peptide than other SIV-specific CTLs. Interestingly, CTLs that require low peptide concentrations for stimulation (high

functional avidity) are particularly effective at controlling other viral infections. Our results suggest that acute viral **escape** from CTLs is a hallmark of SIV infection and that CTLs with high functional avidity can rapidly select for **escape** variants.

L34 ANSWER 20 OF 98 MEDLINE on STN
2002161341. PubMed ID: 11884484. A novel approach to the analysis of specificity, clonality, and frequency of **HIV**-specific T cell responses reveals a potential mechanism for control of viral **escape**. Douek Daniel C; Betts Michael R; Brenchley Jason M; Hill Brenna J; Ambrozak David R; Ngai Ka-Leung; Karandikar Nitin J; Casazza Joseph P; Koup Richard A. (Department of Experimental Transplantation and Immunology, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA.. ddouek@mail.nih.gov) . Journal of immunology (Baltimore, Md. : 1950), (2002 Mar 15) 168 (6) 3099-104. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB **Escape** from the **CD8**(+) T cell response through epitope mutations can lead to loss of immune control of **HIV** replication. Theoretically, **escape** from **CD8**(+) T cell recognition is less likely when multiple TCRs target individual MHC/peptide complexes, thereby increasing the chance that amino acid changes in the epitope could be tolerated. We studied the **CD8**(+) T cell response to six immunodominant epitopes in five **HIV**-infected subjects using a novel approach combining peptide stimulation, cell surface cytokine capture, flow cytometric sorting, anchored RT-PCR, and real-time quantitative clonotypic TCR tracking. We found marked variability in the number of clonotypes targeting individual epitopes. One subject recognized a single epitope with six clonotypes, most of which were able to recognize and lyse cells expressing a major epitope variant that arose. Additionally, multiple clonotypes remained expanded during the course of infection, irrespective of epitope variant frequency. Thus, **CD8**(+) T cells comprising multiple TCR clonotypes may expand in vivo in response to individual epitopes, and may increase the ability of the response to recognize virus **escape** mutants.

L34 ANSWER 21 OF 98 MEDLINE on STN
2002155188. PubMed ID: 11886261. **HIV**-1 Vpr does not inhibit **CTL**-mediated apoptosis of **HIV**-1 infected cells. Lewinsohn Deborah A; Lines Rebecca; Lewinsohn David M; Riddell Stanley R; Greenberg Philip D; Emerman Michael; Bartz Steven R. (Department of Pediatrics, Oregon Health and Sciences University, 707 SW Gaines Road, CDRCP, Portland, OR 97201, USA.. lewinsde@ohsu.edu) . Virology, (2002 Mar 1) 294 (1) 13-21. Journal code: 0110674. ISSN: 0042-6822. Pub. country: United States. Language: English.

AB **HIV**-1 infected persons develop a robust **CTL** response to **HIV** antigens, yet **HIV**-1 is able to evade this host response and successfully replicate. The mechanism(s) of **evasion** is not completely defined but has been suggested to include resistance of infected cells to **CTL**-mediated apoptosis. The **HIV**-1 Vpr protein induces G2 arrest by indirectly inhibiting activation of cyclin B/p34cdc2 kinase. Granzyme B, the principle mediator of **CTL**-induced apoptosis, prematurely activates this same kinase complex. Therefore, we assessed the susceptibility of **HIV**-1 infected cells to **CTL**-mediated apoptosis to determine whether the expression of Vpr protected the infected cells from **CTL**-induced apoptosis. Antigen-specific **CD8**(+) **CTL** were able to induce apoptosis in **HIV**-1 infected cells and cells labeled with peptide corresponding to the **CTL** epitope with equivalent efficiency. This demonstrates that neither **HIV**-1 Vpr nor any other **HIV** protein directly inhibits **CTL** effector functions. Furthermore, we confirm that **HIV**-1 Nef is able to provide partial protection from **CTL** recognition of infected cells. Thus, the inability of **CTL** to control **HIV**-1 infection is likely not due to direct inhibition of **CTL**-mediated apoptosis.

L34 ANSWER 22 OF 98 MEDLINE on STN
2002086186. PubMed ID: 11799157. Nef-mediated resistance of **human immunodeficiency virus** type 1 to antiviral **cytotoxic T**

lymphocytes. Yang Otto O; Nguyen Phuong Thi; Kalams Spyros A; Dorfman Tanya; Gottlinger Heinrich G; Stewart Sheila; Chen Irvin S Y; Threlkeld Steven; Walker Bruce D. (Division of Infectious Diseases and AIDS Institute, UCLA Medical Center, Los Angeles, California 90095, USA.. oyang@mednet.ucla.edu) . Journal of virology, (2002 Feb) 76 (4) 1626-31. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Although Nef has been proposed to effect the **escape** of **human immunodeficiency virus** type 1 (**HIV**-1) from **cytotoxic T lymphocytes** (**CTL**) through downmodulation of major histocompatibility complex class I molecules, little direct data have been presented previously to support this hypothesis. By comparing nef-competent and nef-deleted **HIV**-1 strains in an in vitro coculture system, we demonstrate that the presence of this viral accessory gene leads to impairment of the ability of **HIV**-1-specific **CTL** clones to suppress viral replication. Furthermore, inhibition by genetically modified **CTL** that do not require major histocompatibility complex class I-presented antigen (expressing the CD4 T-cell receptor [TCR] zeta-chain hybrid receptor) is similar for both nef-competent and -deleted strains, indicating that Nef does not impair the effector functions of **CTL** but acts at the level of TCR triggering. In contrast, we note that another accessory gene, vpr, does not induce resistance of **HIV**-1 to suppression by **CTL** clones. We conclude that Nef (and not Vpr) contributes to functional **HIV**-1 immune **evasion** and that this effect is mediated by diminished antigen presentation to **CTL**.

L34 ANSWER 23 OF 98 MEDLINE on STN
2002016363. PubMed ID: 11430595. Reactivation and role of HHV-8 in Kaposi's sarcoma initiation. Ensoli B; Sturzl M; Monini P. (Laboratory of Virology, Istituto Superiore di Sanita, Rome, Italy.. ensoli@iss.it) . Advances in cancer research, (2001) 81 161-200. Ref: 230. Journal code: 0370416. ISSN: 0065-230X. Pub. country: United States. Language: English.

AB Kaposi's sarcoma (KS) is an angioproliferative disease occurring in several clinical-epidemio-logic forms but all associated with infection by the human herpesvirus-8 (HHV-8). At least in early stages, KS is a reactive disease associated with a state of immune dysregulation characterized by **CD8**+ T-cell activation and production of Th1-type inflammatory cytokines (IC) that precedes lesion development. In fact, evidence indicates that IC can trigger lesion formation by inducing the activation of endothelial cells that leads to adhesion and tissue extravasation of lymphomonocytes, spindle cell formation, and angiogenesis, and HHV-8 reactivation that, in turn, leads to virus spread to all circulating cell types and virus dissemination into tissues. Due to virus **escape** mechanisms and deficient immune responses toward HHV-8, virus reactivation and spread are not controlled by the immune system but induce immune responses that may paradoxically exacerbate the reactive process. The virus is recruited into "activated" tissue sites where it finds an optimal environment for growth. In fact, viral load is very low in early lesions, whereas almost all spindle cells are infected in late-stage lesions. Although early KS is a reactive process of polyclonal nature that can regress, in time and in the presence of immunodeficiency, it can progress to a true sarcoma. This is likely due to the long-lasting expression of HHV-8 latency genes in spindle cells associated with the deregulated expression of oncogenes and oncosuppressor genes and, for AIDS-KS, with the effects of the **HIV**-1 Tat protein.

L34 ANSWER 24 OF 98 MEDLINE on STN
2001610653. PubMed ID: 11685220. Cytomegalovirus: from **evasion** to suppression?. Lehner P J; Wilkinson G W. Nature immunology, (2001 Nov) 2 (11) 993-4. Journal code: 100941354. ISSN: 1529-2908. Pub. country: United States. Language: English.

L34 ANSWER 25 OF 98 MEDLINE on STN
2001571615. PubMed ID: 11679152. Analysis of transition from long-term nonprogressive to progressive infection identifies sequences that may attenuate **HIV** type 1. Fang G; Burger H; Chappey C; Rowland-Jones S;

Visosky A; Chen C H; Moran T; Townsend B; Murray M; Weiser B. (Wadsworth Center, New York State Department of Health, Albany, New York 12201, USA.) AIDS research and human retroviruses, (2001 Oct 10) 17 (15) 1395-404. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB Long-term nonprogressive **human immunodeficiency virus** type 1 (**HIV**-1) infection and its transition to progressive infection presents an opportunity to identify the molecular determinants of **HIV**-1 attenuation and pathogenesis. We studied an individual who underwent a transition from long-term nonprogressive to rapidly progressive infection. Because **HIV**-1 RNA genomes in plasma represent replicating virus, we developed a technique to clone full-length **HIV**-1 RNA genomes from plasma and used this technique to obtain clones from this individual before and during the transition. Most clones assayed were infectious, demonstrating that the RNA genomes encoded viable virus. Analysis of 20 complete **HIV**-1 RNA genomic sequences revealed one major difference between sequences found during the two phases of infection. During the nonprogressive phase, the predominant sequences had a large deletion in an Sp1-binding site and adjacent promoter in the U3 part of the long terminal repeat (LTR); when the infection became progressive, all viruses had intact Sp1 and promoter sequences and were derived from a minor species present earlier. Analysis of 184 clones of the LTR region obtained at five time points spanning a 7-year period confirmed this switch. In an in vitro assay, the deletion downregulated LTR-driven transcription of a reporter gene. In addition, analysis of **cytotoxic T lymphocyte** (**CTL**) epitopes predicted from the complete viral RNA genomes revealed multiple potential **escape** mutants that accumulated by the time of progression. These studies suggest that during the nonprogressive phase, the Sp1 enhancer-promoter deletion is likely to have played a role in decreasing replication, thereby attenuating **HIV**-1. The accumulation of **CTL escape** mutants suggests that a breakdown in immunologic surveillance may have allowed proliferation of intact virus, thus leading to rapid disease progression. These data reveal the viral and immune interactions characterizing a transition from long-term nonprogressive to rapidly progressive infection.

L34 ANSWER 26 OF 98 MEDLINE on STN

2001548908. PubMed ID: 11595297. Mother-to-child transmission of **HIV** infection and **CTL escape** through HLA-A2-SLYNTVATL epitope sequence variation. Goulder P J; Pasquier C; Holmes E C; Liang B; Tang Y; Izopet J; Saune K; Rosenberg E S; Burchett S K; McIntosh K; Barnardo M; Bunce M; Walker B D; Brander C; Phillips R E. (Department of Paediatrics, Nuffield Department of Medicine, Level 7, Room 7615, John Radcliffe Hospital, Oxford OX3 9DU, UK.. philip.goulder@ndm.ox.ac.uk) . Immunology letters, (2001 Nov 1) 79 (1-2) 109-16. Journal code: 7910006. ISSN: 0165-2478. Pub. country: Netherlands. Language: English.

AB **Cytotoxic T lymphocytes** (**CTL**) play a central role in containment of **HIV** infection. **Evasion** of the immune response by **CTL escape** is associated with progression to disease. It is therefore hypothesised that transmitted viruses encode **escape** mutations within epitopes that are required for successful control of viraemia. In order to test this hypothesis, **escape** through the dominant HLA-A2-restricted **CTL** epitope SLYNTVATL (p17 Gag residues 77-85 SL9) in the setting of mother-to-child-transmission (MTCT) was investigated. Initial data from two families in which the **HIV**-infected mother expressed HLA-A*0201 and had transmitted the virus to other family members were consistent with this hypothesis. In addition, analysis of the gag sequence phylogeny in one family demonstrated that **CTL escape** variants can be successfully transmitted both horizontally and vertically. To test the hypothesis further, a larger cohort of transmitting mothers (n=8) and non-transmitters (n=14) were studied. Variation within the SL9 epitope was associated with expression of HLA-A2 (P=0.04) but overall no clear link between variation from the SL9 consensus sequence and MTCT was established. However, the high level of background diversity within p17 Gag served to obscure any possible association between **escape** and MTCT. In conclusion, these studies highlighted the obstacles to demonstrating

CTL escape arising at this particular epitope. Alternative strategies likely to be more definitive are discussed.

L34 ANSWER 27 OF 98 MEDLINE on STN
2001511591. PubMed ID: 11559426. A long-term follow-up of an **HIV** type 1-infected patient reveals a coincidence of Nef-directed **cytotoxic T lymphocyte** effectors and high incidence of epitope-deleted variants. Singh M K; Janvier G; Calvez V; Coulaud P; Riviere Y. (Laboratoire d'Immunopathologie Virale, URA CNRS 1930, Institut Pasteur, 75015 Paris, France.) AIDS research and human retroviruses, (2001 Sep 1) 17 (13) 1265-71. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB **Cytotoxic T lymphocytes** (**CTL**) play a critical role in controlling **human immunodeficiency virus**-1 (**HIV**-1) and simian immunodeficiency virus (SIV) infections. However, in spite of developing a strong **CTL** response most **HIV**-1-infected patients eventually progress to AIDS. Amino acid changes in **CTL** epitope have been previously described and may permit **HIV** to **escape** from **CTL** immune responses. The importance of **CTL** selection pressure in controlling the course of viral evolution in **HIV**-infected patient remains debatable. For over a 10-year period, we longitudinally followed a patient for bulk unstimulated effector (eCTL) and stimulated memory **CTL** responses (mCTL) against the viral proteins Gag, Pol, and Nef. The patient showed a strong **CTL** response against Nef in unstimulated peripheral blood mononuclear cells with a peak during Month 40 of the follow-up. The mCTL response was also higher against Nef than Gag and Pol. PCR amplification and nucleotide sequencing of the plasma viral variants showed a viral variant with the epitope deletion that was detected early during the follow-up and essentially replaced the wild-type virus during the peak eCTL response. These studies support the importance of Nef epitope deletion as a mechanism for **HIV**-1 **escape** from **CTL** immune pressure.

L34 ANSWER 28 OF 98 MEDLINE on STN
2001390819. PubMed ID: 11444872. Introduction of tapasin gene restores surface expression of HLA class I molecules, but not antigen presentation of an **HIV** envelope peptide in a hepatoma cell line. Matsui M; Machida S; Tomiyama H; Takiguchi M; Akatsuka T. (Department of Microbiology, Saitama Medical School, Moroyama-Cho, Iruma-Gun, Saitama 350-0495, Japan.) Biochemical and biophysical research communications, (2001 Jul 13) 285 (2) 508-17. Journal code: 0372516. ISSN: 0006-291X. Pub. country: United States. Language: English.

AB A hepatoma cell line, Hep G2, reveals the diminished HLA class I surface expression and the reduced expression of LMP2, LMP7, and tapasin transcripts, suggesting that the reduced expression of these transcripts may be associated with the low expression of HLA class I molecules. Introduction of tapasin gene dramatically up-regulates the surface expression of HLA class I molecules on Hep G2 cells, and unexpectedly, enhances the expression of LMP2 and LMP7 transcripts as well. Unlike Hep G2, these tapasin-transfected Hep G2 cells are recognized by allo-specific **CTL**. However, the transfectant is unable to endogenously present an **HIV** envelope peptide to an **HIV**-specific **CTL** clone, suggesting that a proteasome-independent antigen processing pathway exists and still remains defective in the transfectant. These data may provide significant evidence that the nonproteasomal antigen processing pathway as well as the proteasomal pathway may be impaired in tumor cells to **escape** immune surveillance performed by **CTL**.
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L34 ANSWER 29 OF 98 MEDLINE on STN
2001374685. PubMed ID: 11431424. The flexibility of the TCR allows recognition of a large set of naturally occurring epitope variants by **HIV**-specific **cytotoxic T lymphocytes**. Buseyne F; Riviere Y. (Laboratoire d'Immunopathologie Virale, URA CNRS 1930, Institut Pasteur, 28 rue du Dr Roux, 75724 Paris Cedex 15, France.) International immunology, (2001 Jul) 13 (7) 941-50. Journal code: 8916182. ISSN: 0953-8178. Pub. country: England: United Kingdom. Language: English.

AB Pathogens attempt to evade immune recognition by expressing mutated antigens. The present study shows that two mechanisms happen in vivo during the course of **HIV** infection to limit the **escape** of antigenic variants from **cytotoxic T lymphocyte** (**CTL**) recognition: recognition of several epitope variants by the same TCR and generation of several **CTL** populations specific for a single epitope but recognizing different variant sequences. We have studied two **CTL** populations directed towards the **HIV**-p24gag amino acids 176--184 QASQEVKNW epitope, presented by HLA-B5301. Both **CTL** populations were derived from a long-term asymptomatic **HIV**-infected child and they express different TCR. Each of the two **CTL** recognizes five of the 10 naturally occurring variants. These variants are distinct for both **CTL** and thus a total of eight variants are recognized. Thus, polyclonality of **CTL** specific for the same epitope but differing in variant sequences recognized may improve the control of variant viruses' replication in vivo. In addition to cross-recognition of several variant epitopes, promiscuous recognition of exogenous peptides complexed to allogeneic HLA-B molecules occurs, showing that the TCR can tolerate amino acid changes on both the peptide and the MHC molecule. This flexibility of the TCR is probably of great importance for control of viruses with high genetic variability, such as **HIV**.

L34 ANSWER 30 OF 98 MEDLINE on STN
2001362110. PubMed ID: 11423257. Biology of Kaposi's sarcoma. Ensoli B; Sgadari C; Barillari G; Sirianni M C; Sturzl M; Monini P. (Laboratory of Virology, Istituto Superiore di Sanita, Rome, Italy.. ensoli@iss.it) . European journal of cancer (Oxford, England : 1990), (2001 Jul) 37 (10) 1251-69. Ref: 136. Journal code: 9005373. ISSN: 0959-8049. Pub. country: England: United Kingdom. Language: English.

AB Kaposi's sarcoma (KS) is an angioproliferative disease occurring in several different clinical-epidemiological forms that, however, share the same histological traits and are all associated with infection by the human herpesvirus 8 (HHV8). KS initiates in a context of immune dysregulation characterised by **CD8**+ T cell activation and the production of Th1-type cytokines that induce a generalised activation of endothelial cells leading to adhesion and tissue extravasation of lympho-monocytes, spindle cell formation and angiogenesis. These phenomena are triggered or enhanced by infection with HHV8 that, in turn, is reactivated by the same cytokines. Productively-infected circulating cells are recruited into 'activated' tissue sites where HHV8 finds an optimal environment for establishing a persistent, latent infection of KS spindle cells (KSC). HHV8 dissemination is favoured by virus **escape** mechanisms and immune dysregulation, and leads to immune responses that are not effective against the virus but, paradoxically, exacerbates the reactive process. Although early KS is a reactive process of polyclonal nature that can regress, in time it can progress in to a true sarcoma. The progression of KS appears to be due to the deregulated expression of oncogenes and oncosuppressor genes, to the long-lasting expression of the HHV8 latency genes and, for AIDS-KS, is promoted by the proliferative and angiogenic effects of the **HIV**-1 Tat protein.

L34 ANSWER 31 OF 98 MEDLINE on STN
2001322341. PubMed ID: 11157057. Clustered mutations in **HIV**-1 gag are consistently required for **escape** from HLA-B27-restricted **cytotoxic T lymphocyte** responses. Kelleher A D; Long C; Holmes E C; Allen R L; Wilson J; Conlon C; Workman C; Shaunak S; Olson K; Goulder P; Brander C; Ogg G; Sullivan J S; Dyer W; Jones I; McMichael A J; Rowland-Jones S; Phillips R E. (Medical Research Council Human Immunology Unit, Institute of Molecular Medicine, John Radcliffe Hospital, Headington, Oxford OX3 9DS, United Kingdom.. kelleher@worf.molbiol.ox.ac.uk) . Journal of experimental medicine, (2001 Feb 5) 193 (3) 375-86. Journal code: 2985109R. ISSN: 0022-1007. Pub. country: United States. Language: English.

AB The immune response to **HIV**-1 in patients who carry human histocompatibility leukocyte antigen (HLA)-B27 is characterized by an immunodominant response to an epitope in p24 gag (amino acids 263-272, KRWIILGLNK). Substitution of lysine (K) or glycine (G) for arginine (R) at **HIV**-1 gag residue 264 (R264K and R264G) results in epitopes that bind

to HLA B27 poorly. We have detected a R264K mutation in four patients carrying HLA-B27. In three of these patients the mutation occurred late, coinciding with disease progression. In another it occurred within 1 yr of infection and was associated with a virus of syncytium-inducing phenotype. In each case, R264K was tightly associated with a leucine to methionine change at residue 268. After the loss of the **cytotoxic T lymphocyte** (**CTL**) response to this epitope and in the presence of high viral load, reversion to wild-type sequence was observed. In a fifth patient, a R264G mutation was detected when **HIV**-1 disease progressed. Its occurrence was associated with a glutamic acid to aspartic acid mutation at residue 260. Phylogenetic analyses indicated that these substitutions emerged under natural selection rather than by genetic drift or linkage. Outgrowth of **CTL escape** viruses required high viral loads and additional, possibly compensatory, mutations in the gag protein.

L34 ANSWER 32 OF 98 MEDLINE on STN
2001280401. PubMed ID: 11363793. Fauci presents new findings on **HIV escape** mechanisms and **HIV** suppressor molecules. Folkers G. NIAID AIDS agenda / National Institute of Allergy and Infectious Diseases, (1996 Mar) 10-1. Journal code: 9432911. Pub. country: United States. Language: English.

AB The National Institute of Allergy and Infectious Diseases (NIAID) director, Anthony S. Fauci, M.D., presented findings at the 3rd Conference on Retroviruses and Opportunistic Infections that may help shed light on how **HIV** escapes the body's immune response following initial infection. NIAID researchers have found that certain subsets of **CD8**+ T cells that are known to fight against **HIV**, called **cytotoxic T lymphocytes** (CTLs), multiply quickly after initial infection and then disappear completely after a short period of work. The research also shows that the CTLs tend to accumulate in the bloodstream rather than the lymph nodes, where the virus is replicating. Dr. Fauci also presented new findings on the **HIV** suppressor molecules. Building on previous work demonstrating that **CD8**+ T cells are able to block **HIV** expression, NIAID researchers have found that cytokine interleukin-2 is a strong inducer of the **CD8** suppressor phenomenon, but interleukin-12 is not. Chemokines suppress in vitro virus replication in cells from **HIV**-infected people by making **CD8**+ T cells secrete three immune-signalling molecules, RANTES, MIP-1alpha and MIP-1B. NIAID researchers found that **CD8**-depleted cells also secrete the three molecules resulting in the conclusion that not all **HIV** suppression is due to **CD8**+ T cells. The researchers have also learned that although the molecules may suppress **HIV** in one model system, they may not do it in another model.

L34 ANSWER 33 OF 98 MEDLINE on STN
2001210620. PubMed ID: 11298454. **HIV**-1 Nef inhibits ASK1-dependent death signalling providing a potential mechanism for protecting the infected host cell. Geleziunas R; Xu W; Takeda K; Ichijo H; Greene W C. (Gladstone Institute of Virology and Immunology, PO Box 419100, San Francisco, California 94141-9100, USA.) Nature, (2001 Apr 12) 410 (6830) 834-8. Journal code: 0410462. ISSN: 0028-0836. Pub. country: England: United Kingdom. Language: English.

AB In vivo infection of lymphatic tissues by the **human immunodeficiency virus** type 1 (**HIV**-1) leads to enhanced apoptosis, which prominently involves uninfected bystander cells. Increased killing of such bystander cells is mediated in part through Nef induction of Fas ligand (FasL) expression on the surface of the virally infected T cells. The subsequent interaction of FasL with Fas (CD95) displayed on neighbouring cells, including **HIV**-1-specific **cytotoxic T lymphocytes**, may lead to bystander cell killing and thus forms an important mechanism of immune **evasion**. As **HIV**-1 also enhances Fas expression on virally infected cells, it is unclear how these hosts avoid rapid cell-autonomous apoptosis mediated through cis ligation of Fas by FasL. Here we show that **HIV**-1 Nef associates with and inhibits apoptosis signal-regulating kinase 1 (ASK1), a serine/threonine kinase that forms a common and key signalling intermediate in the Fas and tumour-necrosis factor-alpha (TNFalpha)

death signalling pathways. The interaction of Nef with ASK1 inhibits both Fas- and TNFalpha-mediated apoptosis, as well as the activation of the downstream c-Jun amino-terminal kinase. Our findings reveal a strategy by which **HIV**-1 Nef promotes the killing of bystander cells through the induction of FasL, while simultaneously protecting the **HIV**-1-infected host cell from these same pro-apoptotic signals through its interference with ASK1 function.

L34 ANSWER 34 OF 98 MEDLINE on STN
2001196574. PubMed ID: 11222694. Macrophage tropism of **human immunodeficiency virus** type 1 facilitates in vivo **escape** from **cytotoxic T-lymphocyte** pressure. Schutten M; van Baalen C A; Guillon C; Huisman R C; Boers P H; Sintnicolaas K; Gruters R A; Osterhaus A D. (Institute of Virology, University Hospital Rotterdam, 3015 GE Rotterdam, The Netherlands.) Journal of virology, (2001 Mar) 75 (6) 2706-9. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Early after seroconversion, macrophage-tropic **human immunodeficiency virus** type 1 (**HIV**-1) variants are predominantly found, even when a mixture of macrophage-tropic and non-macrophage-tropic variants was transmitted. For virus contracted by sexual transmission, this is presently explained by selection at the port of entry, where macrophages are infected and T cells are relatively rare. Here we explore an additional mechanism to explain the selection of macrophage-tropic variants in cases where the mucosa is bypassed during transmission, such as blood transfusion, needle-stick accidents, or intravenous drug abuse. With molecularly cloned primary isolates of **HIV**-1 in irradiated mice that had been reconstituted with a high dose of human peripheral blood mononuclear cells, we found that a macrophage-tropic **HIV**-1 clone escaped more efficiently from specific **cytotoxic T-lymphocyte** (**CTL**) pressure than its non-macrophage-tropic counterpart. We propose that CTLs favor the selective outgrowth of macrophage-tropic **HIV**-1 variants because infected macrophages are less susceptible to **CTL** activity than infected T cells.

L34 ANSWER 35 OF 98 MEDLINE on STN
2001175172. PubMed ID: 11241270. High viral burden in the presence of major **HIV**-specific **CD8**(+) T cell expansions: evidence for impaired **CTL** effector function. Kostense S; Ogg G S; Manting E H; Gillespie G; Joling J; Vandenberghe K; Veenhof E Z; van Baarle D; Jurriaans S; Klein M R; Miedema F. (Department of Clinical Viro-Immunology, CLB Sanquin Blood Supply Foundation & Laboratory for Clinical and Experimental Immunology, Academic Medical Center, Amsterdam, The Netherlands.. S_Kostense@clb.nl) . European journal of immunology, (2001 Mar) 31 (3) 677-86. Journal code: 1273201. ISSN: 0014-2980. Pub. country: Germany: Germany, Federal Republic of. Language: English.

AB To investigate the effect of **HIV**-specific **CD8**(+) T cells on viral plasma load and disease progression, we enumerated HLA-A2-, B8- and B57-restricted **CD8**(+) T cells directed against several **HIV** epitopes in a total of 54 patients by the use of tetrameric HLA-peptide complexes. In patients with high CD4(+) T cell numbers, **HIV**-specific tetramer(+) cells inversely correlated with viral load. Patients with CD4(+) T cell numbers below 400/microl blood, however, carried high viral load despite frequently having high tetramer(+) T cell numbers. This lack of correlation between viral load and tetramer(+) cells did not result from viral **escape** variants, as in only 4 of 13 patients, low frequencies of viruses with mutated epitopes were observed. In 15 patients we measured **CD8**(+) T cell antigen responsiveness to **HIV** peptide stimulation in vitro. FACS analyses showed differential IFN-gamma production of the tetramer(+) cells, and this proportion of IFN-gamma-producing tetramer(+) cells correlated with AIDS-free survival and with T cell maturation to the CD27(-) effector stage. These data show that most **HIV**-infected patients have sustained **HIV**-specific T cell expansions but many of these cells seem not to be functional, leaving the patient with high numbers of non-functional virus-specific **CD8**(+) T cells in the face of high viral burden.

L34 ANSWER 36 OF 98 MEDLINE on STN
2001142669. PubMed ID: 11160158. Late seroconversion in **HIV**-resistant Nairobi prostitutes despite pre-existing **HIV**-specific **CD8**+ responses. Kaul R; Rowland-Jones S L; Kimani J; Dong T; Yang H B; Kiama P; Rostron T; Njagi E; Bwayo J J; MacDonald K S; McMichael A J; Plummer F A. (Department of Medical Microbiology, University of Nairobi, Nairobi, Kenya.. rupertkaul@hotmail.com) . Journal of clinical investigation, (2001 Feb) 107 (3) 341-9. Journal code: 7802877. ISSN: 0021-9738. Pub. country: United States. Language: English.

AB Resistance to **HIV** infection in a small group of Kenyan sex workers is associated with **CD8**+-lymphocyte responses to **HIV cytotoxic T-lymphocyte** (**CTL**) epitopes. Eleven prostitutes meeting criteria for **HIV** resistance seroconverted between 1996 and 1999. The occurrence and specificity of preexisting **HIV**-1 epitope-specific responses were examined using the IFN-gamma enzyme-linked immunospot assay, and any epitopes recognized were cloned and sequenced from the infecting viral isolate. Immunologic and behavioral variables were compared between late seroconverters and persistently uninfected sex worker controls. **HIV**-1 **CTL** epitope responses were present in four of six cases, 5-18 months before seroconversion, and their presence was confirmed by bulk **CTL** culture. A possible viral **escape** mutation was found in one of six epitopes. The key epidemiologic correlate of late seroconversion was a reduction in sex work over the preceding year. In persistently uninfected controls, a break from sex work was associated with a loss of **HIV**-specific **CD8**+ responses. Late seroconversion may occur in **HIV**-1-resistant sex workers despite preceding **HIV**-specific **CD8**+ responses. Seroconversion generally occurs in the absence of detectable **CTL escape** mutations and may relate to the waning of **HIV**-specific **CD8**+ responses due to reduced antigenic exposure.

L34 ANSWER 37 OF 98 MEDLINE on STN
2000473060. PubMed ID: 10852125. Virus and target cell evolution in **human immunodeficiency virus** type 1 infection. Mosier D E. (Department of Immunology, The Scripps Research Institute, La Jolla, CA 92037, USA.. dmosier@scripps.edu) . Immunologic research, (2000) 21 (2-3) 253-8. Ref: 38. Journal code: 8611087. ISSN: 0257-277X. Pub. country: United States. Language: English.

AB **Human immunodeficiency virus** (**HIV**) infection leads to a prolonged struggle between a rapidly evolving viral population and a potent immune response. In the vast majority of infected individuals, the virus wins this struggle. In my laboratory, we focus on understanding both the viral and immune factors that contribute to this outcome. The results of our studies and those of many others indicate that **HIV** can **escape** a potent immune response by a combination of mechanisms including rapid mutation, shedding of decoy antigens, modulation of host major histocompatibility complex, and destruction of **cytotoxic T lymphocytes**. The target cells for viral infection change as the virus evolves to use different chemokine coreceptors for entry. The initial targets are activated and resting memory T cells that express both CD4 and CCR5, but both naive and memory CD4 T cells are targeted by viruses capable of using CXCR4 for entry, and macrophages become the primary target cells when most CD4 T cells are depleted. Compelling evidence is emerging that the availability of target cells for infection is as limiting for the spread of virus as the immune response.

L34 ANSWER 38 OF 98 MEDLINE on STN
2000460997. PubMed ID: 10936092. Defining **CTL**-induced pathology: implications for **HIV**. Wodarz D; Krakauer D C. (Institute for Advanced Study, Olden Lane, Princeton, New Jersey 08540, USA.. wodarz@ias.edu) . Virology, (2000 Aug 15) 274 (1) 94-104. Journal code: 0110674. ISSN: 0042-6822. Pub. country: United States. Language: English.

AB The relationship between virus and host cells is multifactorial and nonlinear. This indicates that the effect of an immune response on infection can lead to several different outcomes. These include severe immunopathology. We seek to define properties of **CTL**-induced pathology

in viral infections and examine the implications for **HIV** disease progression. We find that **CTL**-induced pathology is observed if the rate of viral replication is fast relative to the **CTL** responsiveness of the host. Theoretical predictions are consistent with empirical data on LCMV infection. These conditions are also sufficient to induce pathology in **HIV** infection. However, the absence of **HIV**-specific **CTL** can result in an equivalent depletion of the CD4 T cell pool as a consequence of the short life span of activated T cells. A mathematical model describing the evolution of **HIV** coreceptor usage in the context of lytic and nonlytic **CD8** cell responses might account for the relatively long time span required to result in disease. Viral evolution toward parameter ranges allowing **CTL**-induced pathology is difficult to achieve. It requires the emergence of fast viral replication together with **escape** from nonlytic **CTL** responses. However, according to the model, fast viral replication can result in the evolution of virus strains that are susceptible to chemokine-mediated inhibition of viral replication.

L34 ANSWER 39 OF 98 MEDLINE on STN
2000452725. PubMed ID: 11009106. **CD8** memory, immunodominance, and antigenic **escape**. Wodarz D; Nowak M A. (Institute for Advanced Study, Princeton, NJ 08540, USA.) European journal of immunology, (2000 Sep) 30 (9) 2704-12. Journal code: 1273201. ISSN: 0014-2980. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB Previous theoretical work has suggested that efficient virus control or clearance requires antigen-independent persistence of memory **cytotoxic T lymphocyte** precursors (CTLp), and that failure to generate such memory CTLp can result in persistent infection and eventual loss of virus control. Here we use mathematical models to investigate the relationship between virus control, the clonal composition of the **CTL** response and the chance of the virus to evolve antigenic **escape**. In the presence of efficient memory CTLp, virus is controlled at very low levels by a broad **CTL** response directed against multiple epitopes. In this case, antigenic **escape** of the virus population is expected to take a very long time. On the other hand, if the **CTL** response is short lived in the absence of antigen, virus replicates at higher levels and is only opposed by a narrow **CTL** response, characterized by an immunodominant **CTL** clone. In this case, antigenic **escape** is expected to evolve in a short period of time, resulting in progressive loss of virus control. We discuss our findings in relation to data from **HIV**-1-infected patients.

L34 ANSWER 40 OF 98 MEDLINE on STN
2000429074. PubMed ID: 10925292. Impaired **CTL** recognition of cells latently infected with Kaposi's sarcoma-associated herpes virus. Brander C; Suscovich T; Lee Y; Nguyen P T; O'Connor P; Seebach J; Jones N G; van Gorder M; Walker B D; Scadden D T. (Partners AIDS Research Center and Massachusetts General Hospital Cancer Center, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02129, USA.) Journal of immunology (Baltimore, Md. : 1950), (2000 Aug 15) 165 (4) 2077-83. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB Kaposi's sarcoma-associated herpes virus (KSHV) is a recently identified human gamma2-herpesvirus associated with Kaposi's sarcoma, primary effusion lymphoma, and Castleman's disease. We reasoned that **CTL** responses may provide host defense against this virus, and consequently, KSHV may have evolved strategies to evade the **CTL**-mediated immune surveillance. In this study six B cell lines latently infected with KSHV were found to express reduced levels of HLA class I surface molecules compared with B cell lines transformed by the related gamma-herpesvirus EBV. KSHV-infected cells also required higher concentrations of soluble peptides to induce efficient **CTL**-mediated lysis than control cell lines and were unable to process and/or present intracellularly expressed Ag. Incubation of the KSHV-infected cell lines with high concentrations of soluble HLA class I binding peptides did not restore the deficient HLA class I surface expression. To assess the underlying mechanisms of these phenomena, TAP-1 and TAP-2 gene expression was analyzed. While no

attenuation in TAP 2 expression was observed, TAP 1 expression was significantly reduced in all KSHV cell lines compared with that in controls. These results indicate that KSHV can modulate HLA class I-restricted Ag presentation to **CTL**, which may allow latently infected cells to **escape CTL** recognition and persist in the infected host.

L34 ANSWER 41 OF 98 MEDLINE on STN
2000387895. PubMed ID: 10888632. Short- and long-term clinical outcomes in rhesus monkeys inoculated with a highly pathogenic chimeric simian/**human immunodeficiency virus**. Endo Y; Igarashi T; Nishimura Y; Buckler C; Buckler-White A; Plishka R; Dimitrov D S; Martin M A. (Laboratory of Molecular Microbiology, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20892-0460, USA.) Journal of virology, (2000 Aug) 74 (15) 6935-45. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB A highly pathogenic simian/**human immunodeficiency virus** (SHIV), SHIV(DH12R), isolated from a rhesus macaque that had been treated with anti-human **CD8** monoclonal antibody at the time of primary infection with the nonpathogenic, molecularly cloned SHIV(DH12), induced marked and rapid CD4(+) T cell loss in all rhesus macaques intravenously inoculated with 1.0 50% tissue culture infective dose (TCID(50)) to 4.1 x 10(5) TCID(50)s of virus. Animals inoculated with 650 TCID(50)s of SHIV(DH12R) or more experienced irreversible CD4(+) T lymphocyte depletion and developed clinical disease requiring euthanasia between weeks 12 and 23 postinfection. In contrast, the CD4(+) T-cell numbers in four of five monkeys receiving 25 TCID(50)s of SHIV(DH12R) or less stabilized at low levels, and these surviving animals produced antibodies capable of neutralizing SHIV(DH12R). In the fifth monkey, no recovery from the CD4(+) T cell decline occurred, and the animal had to be euthanized. Viral RNA levels, subsequent to the initial peak of infection but not at peak viremia, correlated with the virus inoculum size and the eventual clinical course. Both initial infection rate constants, k, and decay constants, d, were determined, but only the latter were statistically correlated to clinical outcome. The attenuating effects of reduced inoculum size were also observed when virus was inoculated by the mucosal route. Because the uncloned SHIV(DH12R) stock possessed the genetic properties of a lentivirus quasispecies, we were able to assess the evolution of the input virus swarm in animals surviving the acute infection by monitoring the emergence of neutralization **escape** viral variants.

L34 ANSWER 42 OF 98 MEDLINE on STN
2000212044. PubMed ID: 10748556. Host immune profiles and genotyping analysis of **HIV**-1 among Japanese hemophiliac patients. Sugiura Y; Terunuma H; Yamamoto T; Ishikawa M; Sato J; Toyota T; Iwasaki Y. (Department of Neurology, Fukushima Medical University School of Medicine, Japan.) Fukushima journal of medical science, (1999 Jun) 45 (1) 53-62. Journal code: 0374626. ISSN: 0016-2590. Pub. country: Japan. Language: English.

AB We studied the immune profiles of 21 Japanese hemophiliac patients who had been infected with **human immunodeficiency virus** type 1 (**HIV**-1) by the blood preparations during the 1982-84 period, and carried out the genotyping of **HIV**-1 V3 region for uncultivated peripheral blood mononuclear cells (PBMC) from 8 patients. Ten years after infection, asymptomatic carrier (AC, 14 cases) yet outnumbered those in AIDS related complex (ARC, 4 cases) and AIDS (3 cases), and the CD4+ and **CD8**+ T-cell numbers were not correlated with clinical stages. Macrophage tropic sequences, as identified according to the known tropism determinants, appeared to be more frequent as the CD4+ T-cell numbers were higher. There was no correlation of the cell tropism with the disease stages, however. It might be due to **HIV**-1 of CD4+ T-cells being more productive. The mutation in the V3 region appears to differentially influence the **escape** from antibody attack and clinical stages, and the cell tropism may not be related to the cell immunity of the host.

L34 ANSWER 43 OF 98 MEDLINE on STN

2000185900. PubMed ID: 10688894. Viral persistence in vivo through selection of neutralizing antibody-**escape** variants. Ciurea A; Klenerman P; Hunziker L; Horvath E; Senn B M; Ochsenbein A F; Hengartner H; Zinkernagel R M. (Institute for Experimental Immunology, University Hospital, CH-8091 Zurich, Switzerland.. aciurea@pathol.unizh.ch) . Proceedings of the National Academy of Sciences of the United States of America, (2000 Mar 14) 97 (6) 2749-54. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB Despite initial virus control by **CD8(+) cytotoxic T lymphocytes** (CTLs), noncytopathic or variably cytopathic viruses (e.g., hepatitis B and C viruses, **HIV**) are able to establish persistent infections. The role of neutralizing antibodies (nAbs) in controlling disease progression is unclear. Therefore, the phenomenon of viral **evasion** from the nAb response and its implications for virus persistence remain controversial. Here we demonstrate nAb-mediated viral clearance in **CTL**-deficient mice infected with the prototypic noncytopathic lymphocytic choriomeningitis virus (strain WE). During prolonged **CTL** absence, neutralization-resistant virus mutants were selected in individual mice within 70-90 days. In naive animals infected with these virus variants only low nAb responses were induced, resulting in an increased tendency of virus to persist.

L34 ANSWER 44 OF 98 MEDLINE on STN
2000173876. PubMed ID: 10707087. **HIV**-1 Nef protein binds to the cellular protein PACS-1 to downregulate class I major histocompatibility complexes. Piguet V; Wan L; Borel C; Mangasarian A; Demaurex N; Thomas G; Trono D. (Department of Genetics and Microbiology, Faculty of Medicine, University of Geneva, Geneva 1211, Switzerland.) Nature cell biology, (2000 Mar) 2 (3) 163-7. Journal code: 100890575. ISSN: 1465-7392. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Major-histocompatibility-complex (MHC) proteins are used to display, on the surface of a cell, peptides derived from foreign material - such as a virus - that is infecting that cell. **Cytotoxic T lymphocytes** then recognize and kill the infected cell. The **HIV**-1 Nef protein downregulates the cell-surface expression of class I MHC proteins, and probably thereby promotes immune **evasion** by **HIV**-1. In the presence of Nef, class I MHC molecules are relocalized from the cell surface to the trans-Golgi network (TGN) through as-yet-unknown mechanisms. Here we show that Nef-induced downregulation of MHC-I expression and MHC-I targeting to the TGN require the binding of Nef to PACS-1, a molecule that controls the TGN localization of the cellular protein furin. This interaction is dependent on Nef's cluster of acidic amino acids. A chimaeric integral membrane protein containing Nef as its cytoplasmic domain localizes to the TGN after internalization, in an acidic-cluster- and PACS-1-dependent manner. These results support a model in which Nef relocalizes MHC-I by acting as a connector between MHC-I's cytoplasmic tail and the PACS-1-dependent protein-sorting pathway.

L34 ANSWER 45 OF 98 MEDLINE on STN
2000170323. PubMed ID: 10708050. Natural analogue peptides of an **HIV**-1 GP120 T-helper epitope antagonize response of GP120-specific human CD4 T-cell clones. Fenoglio D; Li Pira G; Lozzi L; Bracci L; Saverino D; Terranova P; Bottone L; Lantero S; Megiovanni A; Merlo A; Manca F. (Advanced Biotechnology Center, San Martino Hospital-University of Genoa, Italy.) Journal of acquired immune deficiency syndromes (1999), (2000 Jan 1) 23 (1) 1-7. Journal code: 100892005. ISSN: 1525-4135. Pub. country: United States. Language: English.

AB Neutralizing antibodies and specific **cytotoxic T lymphocytes (CTL)** may contribute to controlling viral spread, and ideally, to virus clearance in **HIV** infection. Both effector mechanisms depend on specific CD4 T-helper (Th) cells. Nevertheless, **HIV** hypervariability facilitates appearance of **escape** mutants for antibodies and for **CTL** responses. Here we also show that natural mutations (i.e., from sequences of different **HIV** strains) in an immunodominant Th epitope recognized by human CD4 clones specific for the envelope glycoprotein gp120 **escape** CD4 T-cell recognition. Furthermore, several natural analogue peptides exert

an antagonistic function by inhibiting proliferative response of T cells specific to gp120 with a wild-type sequence. If similar events occur in vivo, they may represent an additional **escape** mechanism for **HIV**. In fact, antagonism for CD4 Th response may occur during superinfection with a different strain, or with the appearance of a variant carrying a mutated antagonistic sequence. In both cases, impaired Th cell function could lead to reduced immune control of **HIV** infection by interfering with **CTL** and antibody response.

L34 ANSWER 46 OF 98 MEDLINE on STN
2000069582. PubMed ID: 10602884. Houdini's box: towards an understanding of AIDS virus **escape** from the **cytotoxic T-lymphocyte** response. O'Connor D H; Watkins D I. (Wisconsin Regional Primate Research Center, University of Wisconsin, 1220 Capitol Court, Madison, WI 53715-1299, USA.) Immunogenetics, (1999 Nov) 50 (3-4) 237-41. Ref: 38. Journal code: 0420404. ISSN: 0093-7711. Pub. country: United States. Language: English.

L34 ANSWER 47 OF 98 MEDLINE on STN
2000051289. PubMed ID: 10583444. Nef protein induces differential effects in **CD8**+ cells from **HIV**-1-infected patients. Silvestris F; Camarda G; Del Prete A; Tucci M; Dammacco F. (Department of Biomedical Sciences and Human Oncology, University of Bari, Italy. f.silvestris@dimo.uiba.it) . European journal of clinical investigation, (1999 Nov) 29 (11) 980-91. Journal code: 0245331. ISSN: 0014-2972. Pub. country: ENGLAND: United Kingdom. Language: English.

AB BACKGROUND: The Nef protein of **HIV**-1 is suspected to play a role in the depletion of uninfected CD4+ lymphocytes that leads to AIDS. By contrast its effect on **CD8**+ cells, whose functions are also deregulated during **HIV**-1 infection, is presently unclear. Here we describe a number of derangements induced in vitro by Nef in **CD8**+ cells from **HIV**-1-infected patients. DESIGN: Peripheral lymphocytes from 16 **HIV**-1+ subjects and 9 uninfected individuals were cultivated on a Nef-transfected mouse fibroblast layer exposing the carboxyl-terminal region of the viral protein on cell membrane. The cultures were then measured for both apoptosis and proliferation by subdiploid DNA content and Ki67 expression, respectively, whereas the molecular analysis of purified **CD8**+ cells investigated the Fas-L mRNA levels in Nef-treated CTLs. In addition, we evaluated the Nef-induced variation in the extent of **CD8**+/HLA-DR+ subset, which includes non cytotoxic cells secreting T-cell antiviral factor (CAF) and a soluble factor inhibiting the **HIV**-1 replication. RESULTS: The viral protein induced in peripheral blood lymphocytes (PBL) a moderate tendency to proliferate, as measured by the increment of Ki67 antigen, particularly on the **CD8**+ subset of **HIV**-1 infected individuals ($P < 0.05$). This profile was particularly evident in cultures from patients with severe CD4+ lymphopenia and paralleled an apparent expansion of the **CD8**+/CD57+ suppressor cell subset. Molecular analysis of purified **CD8**+ cells revealed a defective expression of Fas-L mRNA in Nef-cultured CTLs, whereas the viral protein exerted a down modulatory effect on the **CD8**+/HLA-DR+ subset ($P < 0.05$), thus suggesting a potential inhibition of CAF. CONCLUSIONS: These results support a potential role of Nef in the progression of **HIV**-1 infection as a number of cellular functions are affected in the **CD8**+ subset. In particular, the defective functions of **CD8**+ cells induced by the viral protein could contribute, at least partly, to the **escape** of **HIV**-1 from the immune control of these cells.

L34 ANSWER 48 OF 98 MEDLINE on STN
2000026000. PubMed ID: 10556818. Selective pressure exerted by immunodominant **HIV**-1-specific **cytotoxic T lymphocyte** responses during primary infection drives genetic variation restricted to the cognate epitope. Soudeyns H; Paolucci S; Chappey C; Daucher M B; Graziosi C; Vaccarezza M; Cohen O J; Fauci A S; Pantaleo G. (Laboratory of AIDS Immunopathogenesis, Department of Internal Medicine,Centre hospitalier universitaire vaudois, Lausanne, Switzerland.) European journal of immunology, (1999 Nov) 29 (11) 3629-35. Journal code: 1273201. ISSN: 0014-2980. Pub. country: GERMANY: Germany, Federal Republic of. Language:

English.

AB HIV-specific **cytotoxic T lymphocytes** (CTL) play a central role in the control of **HIV**-1 replication during primary infection. It has been hypothesized that the appearance of **CTL escape** mutants represents an important mechanism by which **HIV**-1 escapes the host cell-mediated immune response. However, evidences for a direct relationship between **CTL** responses and emergence of **CTL escape** mutants are still limited. Here we report detailed longitudinal analysis of DNA sequence variation performed over the entire **HIV**-1 envelope in two subjects during primary **HIV** infection. Estimates of the frequencies of synonymous (ds) and non-synonymous (dN) nucleotide substitutions were used to identify regions of the **HIV**-1 envelope which were subjected to significant levels of selective pressure. These regions were shown to comprise defined epitopes recognized by **CTL**. Furthermore, dN mutation fixed within these epitopes effectively abolished recognition by the host **CTL** response. These results provide compelling evidence that the **CTL** epitope mutations directly resulted from the selective pressure exerted by the virus-specific cytotoxic response.

L34 ANSWER 49 OF 98 MEDLINE on STN
2000015179. PubMed ID: 10545982. The great **escape** - AIDS viruses and immune control. Goulder P J; Walker B D. Nature medicine, (1999 Nov) 5 (11) 1233-5. Journal code: 9502015. ISSN: 1078-8956. Pub. country: United States. Language: English.

AB Many studies have been designed to address the role of **CTL** immune **escape** in **HIV**-1 infection, but have not given conclusive answers. Now, an elegant longitudinal analysis clearly demonstrates that progression to disease in SIV-infected macaques is associated with **evasion** of the **CTL** response (pages 1270-1276).

L34 ANSWER 50 OF 98 MEDLINE on STN
1999412391. PubMed ID: 10482626. Mosaic structure of the **human immunodeficiency virus** type 1 genome infecting lymphoid cells and the brain: evidence for frequent in vivo recombination events in the evolution of regional populations. Morris A; Marsden M; Halcrow K; Hughes E S; Brettle R P; Bell J E; Simmonds P. (Department of Medical Microbiology, University of Edinburgh, Edinburgh EH8 9AG, Edinburgh EH4 2XU, United Kingdom.) Journal of virology, (1999 Oct) 73 (10) 8720-31. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB In addition to immunodeficiency, **human immunodeficiency virus** type 1 (**HIV**-1) can cause cognitive impairment and dementia through direct infection of the brain. To investigate the adaptive process and timing of **HIV**-1 entry into the central nervous system, we carried out an extensive genetic characterization of variants amplified from different regions of the brain and determined their relatedness to those in lymphoid tissue. **HIV**-1 genomes infecting different regions of the brain of one study subject with **HIV** encephalitis (HIVE) had a mosaic structure, being assembled from different combinations of evolutionarily distinct lineages in p17(gag), pol, individual hypervariable regions of gp120 (V1/V2, V3, V4, and V5), and gp41/nef. Similar discordant phylogenetic relationships were observed between p17(gag) and V3 sequences of brain and lymphoid tissue from three other individuals with HIVE. The observation that different parts of the genome of **HIV** infecting a particular tissue can have different evolutionary histories necessarily limits the conclusions that can be drawn from previous studies of the compartmentalization of distinct **HIV** populations in different tissues, as these have been generally restricted to sequence comparisons of single subgenomic regions. The complexity of viral populations in the brain produced by recombination could provide a powerful adaptive mechanism for the spread of virus with new phenotypes, such as antiviral resistance or **escape** from **cytotoxic T-cell** recognition into existing tissue-adapted virus populations.

L34 ANSWER 51 OF 98 MEDLINE on STN
1999388926. PubMed ID: 10461830. Accumulation of specific amino acid substitutions in HLA-B35-restricted **human immunodeficiency virus** type 1 **cytotoxic T lymphocyte** epitopes. Kawana A; Tomiyama H;

Taniguchi M, Shioda T, Nakamura T, Iwamoto A. (Department of Infectious Diseases, Institute of Medical Science, University of Tokyo, Japan.) AIDS research and human retroviruses, (1999 Aug 10) 15 (12) 1099-107. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB HLA is one of the genetic factors that influence the clinical course of **HIV**-1 infection, and patients with HLA-B35 are prone to rapid disease progression. Nine viral epitopes that are recognized by **cytotoxic T lymphocytes** (CTLs) in an HLA-B35-restricted manner were determined. To examine how **HIV**-1 sequences are selected by CTLs in vivo, we sequenced the nine **CTL** epitopes of the virus in patient plasma. Here we show that certain amino acid substitutions at three epitopes were observed with significantly higher frequency in HLA-B35-positive patients than in HLA-B35-negative patients. By performing experiments with **CTL** clones established from the HLA-B35-positive patients, it was determined that one of the three substitutions was probably an **escape** mutation. However, concerning the other two epitopes, representative **CTL** clones killed target cells pulsed with mutant peptides as efficiently as those pulsed with wild-type peptides, suggesting that CTLs that can be established in vitro are not functioning properly in vivo. Amino acid sequence drift in all HLA-B35-restricted epitopes was rare during the observation period (1 year). Our results may have relevance in understanding the rapid clinical progression in HLA-B35-positive patients.

L34 ANSWER 52 OF 98 MEDLINE on STN

1999330435. PubMed ID: 10403641. The selective downregulation of class I major histocompatibility complex proteins by **HIV**-1 protects **HIV**-infected cells from NK cells. Cohen G B; Gandhi R T; Davis D M; Mandelboim O; Chen B K; Strominger J L; Baltimore D. (Department of Biology, Massachusetts Institute of Technology, Cambridge 02139, USA.) Immunity, (1999 Jun) 10 (6) 661-71. Journal code: 9432918. ISSN: 1074-7613. Pub. country: United States. Language: English.

AB To avoid detection by **CTL**, **HIV** encodes mechanisms for removal of class I MHC proteins from the surface of infected cells. However, class I downregulation potentially exposes the virus-infected cell to attack by NK cells. Human lymphoid cells are protected from NK cell cytotoxicity primarily by HLA-C and HLA-E. We present evidence that **HIV**-1 selectively downregulates HLA-A and HLA-B but does not significantly affect HLA-C or HLA-E. We then identify the residues in HLA-C and HLA-E that protect them from **HIV** down-regulation. This selective downregulation allows **HIV**-infected cells to avoid NK cell-mediated lysis and may represent for **HIV** a balance between **escape** from **CTL** and maintenance of protection from NK cells. These results suggest that subpopulations of **CTL** and NK cells may be uniquely suited for combating **HIV**.

L34 ANSWER 53 OF 98 MEDLINE on STN

1999327264. PubMed ID: 10399065. **HIV**'s **evasion** of the cellular immune response. Collins K L; Baltimore D. (Department of Medicine, University of Michigan, Ann Arbor, USA.) Immunological reviews, (1999 Apr) 168 65-74. Ref: 68. Journal code: 7702118. ISSN: 0105-2896. Pub. country: Denmark. Language: English.

AB Despite a strong **cytotoxic T-lymphocyte** (**CTL**) response directed against viral antigens, untreated individuals infected with the **human immunodeficiency virus** (**HIV**-1) develop AIDS. We have found that primary T cells infected with **HIV**-1 downregulate surface MHC class I antigens and are resistant to lysis by HLA-A2-restricted **CTL** clones. In contrast, cells infected with an **HIV**-1 in which the nef gene is disrupted are sensitive to CTLs in an MHC and peptide-specific manner. In primary T cells HLA-A2 antigens are downmodulated more dramatically than total MHC class I antigens, suggesting that nef selectively downmodulates certain MHC class I antigens. In support of this, studies on cells expressing individual MHC class I alleles have revealed that nef does not downmodulate HLA-C and HLA-E antigens. This selective downmodulation allows infected cells to maintain resistance to certain natural killer cells that lyse infected cells expressing low levels of MHC class I

antigens. Downmodulation of MHC class I HLA A2 antigens occurs not only in primary T cells, but also in B and astrocytoma cell lines. No effect of other **HIV**-1 accessory proteins such as vpu and vpr was observed. Thus Nef is a protein that may promote **escape** of **HIV**-1 from immune surveillance.

L34 ANSWER 54 OF 98 MEDLINE on STN
1999218520. PubMed ID: 10202022. Persistent **HIV**-1-specific **CTL** clonal expansion despite high viral burden post in utero **HIV**-1 infection. Brander C; Goulder P J; Luzuriaga K; Yang O O; Hartman K E; Jones N G; Walker B D; Kalams S A. (AIDS Research Center and Infectious Disease Unit, Massachusetts General Hospital, Harvard Medical School, Charlestown, MA 02129, USA.) Journal of immunology (Baltimore, Md. : 1950), (1999 Apr 15) 162 (8) 4796-800. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB To address the issue of clonal exhaustion in humans, we monitored HLA class I-restricted, epitope-specific **CTL** responses in an in utero **HIV**-1-infected infant from 3 mo through 5 years of age. Serial functional **CTL** precursor assays demonstrated persistent, vigorous, and broadly directed **HIV**-1 specific **CTL** activity with a dominant response against an epitope in **HIV**-1 Gag-p17 (SLYNTVATL, aa 77-85). A clonal **CTL** response directed against the immunodominant, HLA-A*0201-restricted epitope was found to persist over the entire observation period, as shown by TCR analysis of cDNA libraries generated from PBMC. The analysis of autologous viral sequences did not reveal any **escape** mutations within the targeted epitope, and viral load measurement indicated ongoing viral replication. Furthermore, inhibition of viral replication assays indicated that the epitope was properly processed from autologous viral protein. These data demonstrate that persistent exposure to high levels of viral Ag does not necessarily lead to clonal exhaustion and that epitope-specific clonal **CTL** responses induced within the first weeks of life can persist for years without inducing detectable viral **escape** variants.

L34 ANSWER 55 OF 98 MEDLINE on STN
1999192796. PubMed ID: 10092836. Molecular and functional analysis of a conserved **CTL** epitope in **HIV**-1 p24 recognized from a long-term nonprogressor: constraints on immune **escape** associated with targeting a sequence essential for viral replication. Wagner R; Leschonsky B; Harrer E; Paulus C; Weber C; Walker B D; Buchbinder S; Wolf H; Kalden J R; Harrer T. (Institute of Medical Microbiology, University of Regensburg, Germany.) Journal of immunology (Baltimore, Md. : 1950), (1999 Mar 15) 162 (6) 3727-34. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB It has been hypothesized that sequence variation within **CTL** epitopes leading to immune **escape** plays a role in the progression of **HIV**-1 infection. Only very limited data exist that address the influence of biologic characteristics of **CTL** epitopes on the emergence of immune **escape** variants and the efficiency of suppression **HIV**-1 by **CTL**. In this report, we studied the effects of **HIV**-1 **CTL** epitope sequence variation on **HIV**-1 replication. The highly conserved HLA-B14-restricted **CTL** epitope DRFYKTLRAE in **HIV**-1 p24 was examined, which had been defined as the immunodominant **CTL** epitope in a long-term nonprogressing individual. We generated a set of viral mutants on an HX10 background differing by a single conservative or nonconservative amino acid substitution at each of the P1 to P9 amino acid residues of the epitope. All of the nonconservative amino acid substitutions abolished viral infectivity and only 5 of 10 conservative changes yielded replication-competent virus. Recognition of these epitope sequence variants by **CTL** was tested using synthetic peptides. All mutations that abrogated **CTL** recognition strongly impaired viral replication, and all replication-competent viral variants were recognized by **CTL**, although some variants with a lower efficiency. Our data indicate that this **CTL** epitope is located within a viral sequence essential for viral replication. Targeting **CTL** epitopes within functionally important regions of the **HIV**-1 genome could limit the chance of immune **evasion**.

L34 ANSWER 56 OF 98 MEDLINE on STN
1999129881. PubMed ID: 9933101. Dendritic cells transfected with the nef genes of **HIV**-1 primary isolates specifically activate **cytotoxic T lymphocytes** from seropositive subjects. Chassin D; Andrieu M; Cohen W; Culmann-Penciolelli B; Ostankovitch M; Hanau D; Guillet J G. (Laboratoire d'Immunologie des Pathologies Infectieuses et Tumorales, INSERM U445, ICGM, Universite Rene Descartes, Paris, France.. chassin@icgm.cochin.inserm.fr) . European journal of immunology, (1999 Jan) 29 (1) 196-202. Journal code: 1273201. ISSN: 0014-2980. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB The **HIV**-1 Nef protein down-modulates surface expression of MHC class I proteins. Primary infected T lymphocytes thus **escape** lysis by **cytotoxic T lymphocytes** (**CTL**). In contrast, during **HIV**-1 infection there are strong **CTL** responses to several **HIV** proteins, and there is mounting evidence that **CTL** are critical for controlling the virus. The present study was carried out to assess Nef protein-cell interaction as it occurs in naturally infected antigen-presenting cells. To evaluate the presentation of peptides derived from viral antigen to **CTL**, we transfected nef genes obtained from peripheral blood mononuclear cells of **HIV**-1-seropositive subjects into dendritic cells isolated from monocytes of healthy donors. We demonstrate that expression and subsequent processing of Nef by transfected dendritic cells did not alter the presentation of an immunodominant epitope of Nef to **CTL** of **HIV**+ subjects. However, mutations in nef gene sequences from primary isolates may abolish this presentation by a mechanism that probably interferes with protein processing.

L34 ANSWER 57 OF 98 MEDLINE on STN
1999037105. PubMed ID: 9819670. **CD8** lymphocytes in **HIV** infection: helpful and harmful. Famularo G; Moretti S; Marcellini S; Nucera E; De Simone C. (Department of Experimental Medicine, University of L'Aquila, Italy.) Journal of clinical & laboratory immunology, (1997) 49 (1) 15-32. Ref: 97. Journal code: 7808987. ISSN: 0141-2760. Pub. country: SCOTLAND: United Kingdom. Language: English.

AB The part played by **CD8** lymphocytes in the pathogenesis of **human immunodeficiency virus** infection (**HIV**) is much disputed and the relevant issue of the controversy ranges as to whether the functional activity of these cells is beneficial or detrimental to the host. Even though **CD8** cells could efficiently suppress **HIV** replication through both major histocompatibility complex (MHC)-restricted cytotoxic killing of infected cells, particularly during primary infection, and **HIV**-suppressing soluble factors, there is evidence that tissue-infiltrating **CD8** lymphocytes mediate injury in several organs of **HIV**-infected subjects. Furthermore, **CD8** lymphocytes could contribute to the destruction of CD4 cells in vivo. Of note, the virus has the capability to **escape** the recognition by cytotoxic **CD8** cells and the cytotoxic activity of **CD8** cells and their counts decline with evolving **HIV** infection. Several mechanisms are proposed to explain this latter finding, including the direct in vivo infection of **CD8** cells by the virus. It is likely that early during the course of **HIV** infection when viral loads are generally low an efficient **CD8** cell response can control **HIV** replication whereas in subjects with evolving disease, who have very high viral loads, **CD8** lymphocytes remove essential components of the immune response and mediate tissue injury.

L34 ANSWER 58 OF 98 MEDLINE on STN
1999008552. PubMed ID: 9794421. Recognition of two overlapping **CTL** epitopes in **HIV**-1 p17 by **CTL** from a long-term nonprogressing **HIV**-1-infected individual. Harrer T; Harrer E; Barbosa P; Kaufmann F; Wagner R; Bruggemann S; Kalden J R; Feinberg M; Johnson R P; Buchbinder S; Walker B D. (Department of Medicine III with Institute of Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany.. Thomas.Harrer@med3.med.uni-erlangen.de) . Journal of immunology (Baltimore, Md. : 1950), (1998 Nov 1) 161 (9) 4875-81. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB HIV-1 infection has been shown to elicit strong **CTL** responses in some infected persons, but few data are available regarding the relationship between targeted epitopes and in vivo viral quasispecies. In this study, we examined the **CTL** response in a person infected for 15 yr with a CD4 count persistently >500 cells/microl. The dominant in vivo activated **CTL** response was directed against two overlapping Gag **CTL** epitopes in an area of p17 known to be essential for viral replication. The 9-mer SLYNTVATL (amino acids 77-85) was recognized in conjunction with HLA-A2, whereas the overlapping 8-mer TLYCVHQR (amino acids 83-91) was recognized by HLA-A11-restricted **CTL**. Analysis of in vivo virus sequences both in PBMC and plasma revealed the existence of sequence variation in this region, which did not affect viral replication in vitro, but decreased recognition by the A11-restricted **CTL** response, with maintenance of the A2-restricted response. These results indicate that an essential region of the p17 protein can be simultaneously targeted by **CTL** through two different HLA molecules, and that immune **escape** from **CTL** recognition can occur without impairing viral replication. In addition, they demonstrate that Ag processing can allow for presentation of overlapping epitopes in the same infected cell, which can be affected quite differently by sequence variation.

L34 ANSWER 59 OF 98 MEDLINE on STN
1999003700. PubMed ID: 9787432. Conservation of **cytotoxic T lymphocyte** (**CTL**) epitopes as a host strategy to constrain parasite adaptation: evidence from the nef gene of **human immunodeficiency virus** 1 (**HIV**-1). da Silva J; Hughes A L. (Department of Biology, Pennsylvania State University, University Park 16802, USA.) Molecular biology and evolution, (1998 Oct) 15 (10) 1259-68. Journal code: 8501455. ISSN: 0737-4038. Pub. country: United States. Language: English.

AB Host **cytotoxic T lymphocytes** (CTLs) that recognize specific viral peptides (epitopes) are thought to provide the most effective control of viral replication and spread. However, viruses may **escape** this recognition through mutations in **CTL** epitopes. We tested the hypothesis that, as an adaptation on the part of the host to constrain parasite **escape** from immune control, class I major histocompatibility complex (MHC) molecules present peptides that are derived from conserved regions of foreign proteins to CTLs. We did this by estimating the relative conservation of **CTL** epitopes of the functionally important Nef protein of **human immunodeficiency virus** 1 (**HIV**-1) and relating this to the structure and function of the protein. In comparisons among sequences from several **HIV**-1 subtypes and both major groups, **CTL** epitopes had lower rates of nonsynonymous nucleotide substitution per site than did the remainder of the protein, indicating the relative conservation of these epitopes. In contrast, helper T-cell epitopes were as conserved as, and monoclonal antibody epitopes less conserved than, the remainder of the protein. The conservation of **CTL** epitopes is apparently due to their derivation from functionally important domains of Nef, since **CTL** epitopes coincide with these domains and these domains are conserved relative to the remainder of the protein, in contrast to secondary structural elements, which are not. Recent studies provide evidence of **CTL** selection on **HIV**-1 epitopes, but the variational range of viral **escape** mutants appears to be limited by functional constraints on the protein regions from which epitopes are derived. The presentation of conserved foreign peptides to CTLs by class I MHC molecules may be a general adaptation of vertebrate hosts to constrain the adaptation of their intracellular parasites.

L34 ANSWER 60 OF 98 MEDLINE on STN
1999001851. PubMed ID: 9785672. Anti-apoptotic strategies of lymphotropic viruses. Meinl E; Fickenscher H; Thome M; Tschopp J; Fleckenstein B. (Institut fur Klinische und Molekulare Virologie, Universitat Erlangen-Nurnberg, Germany.. ermeinl@viro.med.uni-erlangen.de) . Immunology today, (1998 Oct) 19 (10) 474-9. Ref: 55. Journal code: 8008346. ISSN: 0167-5699. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Induction of apoptosis of virus-infected cells is an important host cell

defence mechanism. However, some viruses have incorporated genes that encode anti-apoptotic proteins or modulate the expression of cellular regulators of apoptosis. Here, Edgar Meinl and colleagues discuss recent evidence that viral interference with host cell apoptosis leads to enhanced viral replication, and to **evasion** of **cytotoxic T-cell** effects.

L34 ANSWER 61 OF 98 MEDLINE on STN
1998361236. PubMed ID: 9697771. Original antigenic sin impairs **cytotoxic T lymphocyte** responses to viruses bearing variant epitopes. Klenerman P; Zinkernagel R M. (Institute for Experimental Immunology, University Hospital, Zurich, Switzerland.) Nature, (1998 Jul 30) 394 (6692) 482-5. Journal code: 0410462. ISSN: 0028-0836. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Some viruses, including **human immunodeficiency virus** (**HIV**) and hepatitis B virus (HBV) in humans, and lymphocytic choriomeningitis virus (LCMV) in mice, are initially controlled by **cytotoxic T lymphocytes** (CTLs), but may subsequently **escape** through mutation of the relevant T-cell epitope. Some of these mutations preserve the normal binding to major histocompatibility complex class I molecules, but present an altered surface to the T-cell antigen receptor. The exact role of these so-called altered peptide ligands in vivo is not clear. Here we report that mice primed with LCMV-WE strain respond to a subsequent infection by WE-derived **CTL** epitope variants with a **CTL** response directed against the initial epitope rather than against the new variant epitope. This phenomenon of 'original antigenic sin' was initially described in influenza and is an asymmetric pattern of protective antibody crossreactivity determined by exposure to previously existing strains, which may therefore extend to some **CTL** responses. Original antigenic sin by **CTL** leads to impaired clearance of variant viruses infecting the same individual and so may enhance the immune **escape** of mutant viruses evolving in an individual host.

L34 ANSWER 62 OF 98 MEDLINE on STN
1998332797. PubMed ID: 9665869. Virus variation, **escape** from **cytotoxic T lymphocytes** and human retroviral persistence. Gould K G; Bangham C R. (Department of Immunology, Imperial College School of Medicine, Norfolk Place, London, W2 1PG, UK.) Seminars in cell & developmental biology, (1998 Jun) 9 (3) 321-8. Ref: 44. Journal code: 9607332. ISSN: 1084-9521. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Viruses use a variety of mechanisms to **escape** recognition by **cytotoxic T lymphocytes** (**CTL**). The available evidence suggests that the main mechanisms of **CTL escape** caused by viral sequence variation are loss of epitope binding to MHC molecules or altered recognition by T cell receptors. These types of mutations occur in both **human immunodeficiency virus** type 1 (**HIV**-1) and human T cell leukaemia virus type 1 (HTLV-1) infections. In **HIV**-1, **CTL escape** is one factor that may cause progression of disease. In HTLV-1, however, **CTL escape** mutants never predominate in the viral population.
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L34 ANSWER 63 OF 98 MEDLINE on STN
1998189358. PubMed ID: 9512422. Antigen-specific release of beta-chemokines by anti-**HIV**-1 **cytotoxic T lymphocytes**. Price D A; Sewell A K; Dong T; Tan R; Goulder P J; Rowland-Jones S L; Phillips R E. (Institute of Molecular Medicine, John Radcliffe Hospital, Oxford, UK.) Current biology : CB, (1998 Mar 12) 8 (6) 355-8. Journal code: 9107782. ISSN: 0960-9822. Pub. country: ENGLAND: United Kingdom. Language: English.

AB A major advance in understanding **human immunodeficiency virus** (**HIV**) biology was the discovery that the beta-chemokines MIP-1 alpha (macrophage inflammatory protein-1 alpha), MIP-1 beta (macrophage inflammatory protein-1 beta) and RANTES (regulated on activation, normal T-cell expressed and secreted) inhibit entry of **HIV**-1 into CD4+ cells by blocking the critical interaction between the CCR5 coreceptor and the V3 domain of the viral envelope glycoprotein gp120 [1,2]. **CD8**+ lymphocytes are a major source of beta-chemokines [3], but the stimulus for chemokine release has not been well defined. Here, we have shown that engagement of

CD8+ **cytotoxic T lymphocytes** (CTLs) with **HIV**-1 encoded human leukocyte antigen (HLA) class I-restricted peptide antigens caused rapid and specific release of these beta-chemokines. This release paralleled cytolytic activity and could be attenuated by naturally occurring amino acid variation within the HLA class I-restricted peptide sequence. Epitope variants that bound to appropriate HLA class I molecules but failed to stimulate cytolytic activity in CTLs also failed to stimulate chemokine release. We conclude that signalling through the T-cell receptor (TCR) following binding of antigen results in beta-chemokine release from CTLs in addition to cytolytic activity, and that both responses can be abolished by epitope mutation. These results suggest that antigenic variation within **HIV**-1 might not only allow the host cell to **escape** lysis, but might also contribute to the propagation of infection by failing to activate beta-chemokine-mediated inhibition of **HIV**-1 entry.

L34 ANSWER 64 OF 98 MEDLINE on STN

1998111233. PubMed ID: 9450757. **HIV**-1 Nef protein protects infected primary cells against killing by **cytotoxic T lymphocytes**. Collins K L; Chen B K; Kalams S A; Walker B D; Baltimore D. (Department of Biology, Massachusetts Institute of Technology, Cambridge 02139, USA.) Nature, (1998 Jan 22) 391 (6665) 397-401. Journal code: 0410462. ISSN: 0028-0836. Pub. country: ENGLAND: United Kingdom. Language: English.

AB **Cytotoxic T lymphocytes** (CTLs) lyse virally infected cells that display viral peptide epitopes in association with major histocompatibility complex (MHC) class I molecules on the cell surface. However, despite a strong **CTL** response directed against viral epitopes, untreated people infected with the **human immunodeficiency virus** (**HIV**-1) develop AIDS. To resolve this enigma, we have examined the ability of CTLs to recognize and kill infected primary T lymphocytes. We found that CTLs inefficiently lysed primary cells infected with **HIV**-1 if the viral nef gene product was expressed. Resistance of infected cells to **CTL** killing correlated with nef-mediated downregulation of MHC class I and could be overcome by adding an excess of the relevant **HIV**-1 epitope as soluble peptide. Thus, Nef protected infected cells by reducing the epitope density on their surface. This effect of nef may allow **evasion** of **CTL** lysis by **HIV**-1-infected cells.

L34 ANSWER 65 OF 98 MEDLINE on STN

1998022660. PubMed ID: 9359702. In vivo evolution of **HIV**-1 co-receptor usage and sensitivity to chemokine-mediated suppression. Scarlatti G; Tresoldi E; Bjorndal A; Fredriksson R; Colognesi C; Deng H K; Malnati M S; Plebani A; Siccardi A G; Littman D R; Fenyo E M; Lusso P. (Unit of Immunobiology of HIV, DIBIT, San Raffaele Scientific Institute, Milan, Italy.) Nature medicine, (1997 Nov) 3 (11) 1259-65. Journal code: 9502015. ISSN: 1078-8956. Pub. country: United States. Language: English.

AB Following the identification of the C-C chemokines RANTES, MIP-1alpha and MIP-1beta as major **human immunodeficiency virus** (**HIV**)-suppressive factors produced by **CD8**+ T cells, several chemokine receptors were found to serve as membrane co-receptors for primate immunodeficiency lentiretroviruses. The two most widely used co-receptors thus far recognized, CCR5 and CXCR4, are expressed by both activated T lymphocytes and mononuclear phagocytes. CCR5, a specific RANTES, MIP-1alpha and MIP-1 receptor, is used preferentially by non-MT2-tropic **HIV**-1 and **HIV**-2 strains and by simian immunodeficiency virus (SIV), whereas CXCR4, a receptor for the C-X-C chemokine SDF-1, is used by MT2-tropic **HIV**-1 and **HIV**-2, but not by SIV. Other receptors with a more restricted cellular distribution, such as CCR2b, CCR3 and STRL33, can also function as co-receptors for selected viral isolates. The third variable region (V3) of the gp120 envelope glycoprotein of **HIV**-1 has been fingered as a critical determinant of the co-receptor choice. Here, we document a consistent pattern of evolution of viral co-receptor usage and sensitivity to chemokine-mediated suppression in a longitudinal follow-up of children with progressive **HIV**-1 infection. Viral isolates obtained during the asymptomatic stages generally used only CCR5 as a co-receptor and were inhibited by RANTES, MIP-1alpha and MIP-1beta, but not by SDF-1. By

contrast, the majority of the isolates derived after the progression of the disease were resistant to C-C chemokines, having acquired the ability to use CXCR4 and, in some cases, CCR3, while gradually losing CCR5 usage. Surprisingly, most of these isolates were also insensitive to SDF-1, even when used in combination with RANTES. An early acquisition of CXCR4 usage predicted a poor prognosis. In children who progressed to AIDS without a shift to CXCR4 usage, all the sequential isolates were CCR5-dependent but showed a reduced sensitivity to C-C chemokines. Discrete changes in the V3 domain of gp120 were associated with the loss of sensitivity to C-C chemokines and the shift in co-receptor usage. These results suggest an adaptive evolution of **HIV**-1 in vivo, leading to **escape** from the control of the antiviral C-C chemokines.

L34 ANSWER 66 OF 98 MEDLINE on STN
97437476. PubMed ID: 9292009. Primary induction of human cytotoxic lymphocytes against a synthetic peptide of the **human immunodeficiency virus** type 1 protease. Konya J; Stuber G; Bjorndal A; Fenyo E M; Dillner J. (Karolinska Institute, Microbiology and Tumorbiology Center, Stockholm, Sweden.) Journal of general virology, (1997 Sep) 78 (Pt 9) 2217-24. Journal code: 0077340. ISSN: 0022-1317. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Identification of in vitro immunogenic T-cell epitopes is important for the design of immunotherapeutics targeted to specific antigenic sites. To identify candidate **cytotoxic T-lymphocyte** (**CTL**) epitopes in the protease of **human immunodeficiency virus** type 1 (**HIV**-1) strain MN, we synthesized 9-mer and 10-mer peptides containing the HLA-A*0201 binding motif. Binding affinity of the peptides was measured by HLA-A*0201 up-regulation on T2 cells. Peptides with high binding-affinity were tested for their ability to stimulate primary CTLs from healthy **HIV**-negative blood donors. Peptide-specific CTLs were obtained from five out of six donors by stimulation with a 9-mer (LVGPTPVNI) or a 10-mer (VLVGPTPVNI) peptide derived from a highly conserved amino acid stretch in the C-terminal region of the protease. Addition of peptide-specific CTLs to acutely **HIV**-infected lymphocytes resulted in inhibition of p24gag production. In conclusion, a highly conserved **HIV** protease peptide regularly elicits peptide-specific CTLs. Targeting immune responses against defined epitopes in non-variable regions may be a feasible way to minimize the risk of virus **escape** from immune surveillance.

L34 ANSWER 67 OF 98 MEDLINE on STN
97304245. PubMed ID: 9160517. A clearer distinction between **HIV**-1 paired isolates from peripheral blood mononuclear cells of asymptomatic carriers with and without **CD8**+ T-cells at nef rather than env V3 loci. Zhong Q; Nakaya T; Tateno Y; Fujinaga K; Kameoka M; Tateno M; Ikuta K. (Section of Serology, Hokkaido University, Sapporo, Japan.) Vaccine, (1997 Apr) 15 (5) 497-510. Journal code: 8406899. ISSN: 0264-410X. Pub. country: ENGLAND: United Kingdom. Language: English.

AB In asymptomatic carriers, the vast majority of **human immunodeficiency virus** type 1 (**HIV**-1) infection is non-productive whilst the clinical stage of disease is associated with significant virus expression. Virus-specific **CD8**+ T-cell functions are believed to play a major role in the generation of heterogeneous virus populations and in subsequent disease progression. Here, we prepared two types of **HIV**-1 isolate by culturing whole and **CD8**+ T cell-depleted peripheral blood mononuclear cells (PBMCs) from five asymptomatic carriers. The former is expected to be **escape** variant populations, whereas the latter would be mixed populations including the former viruses. The analyses of Nef and Env V3 sequence variations of viruses in a total of 77 and 44 DNA clones, respectively, allowed a direct comparison to be made of the differences between the paired isolates. Comparison of Nef sequences between the paired isolates showed them to be more distinct in two carriers with a relatively stable CD4/**CD8** ratio (Nos 68 and 69), than in two other carriers with similar CD4/**CD8** ratios (Nos 53 and 57), or in carrier No. 67, which had an extremely lower CD4/**CD8** ratio. By contrast, a distinction between the paired isolates by use of the Env V3 sequences was only apparent in the latter three carriers. These results indicate that

the predominant populations of HIV-1 in Nos 60 and 65 were sensitive to selective pressure from Nef-specific **CD8**+ T-cells, while those in Nos 53, 57, and 67 were sensitive to pressure from V3-specific **CD8**+ T-cells. It is noteworthy that Nos 53 and 57 progressed to an AIDS-related complex shortly and several years after this examination. These data suggest that **HIV**-1-induced pathogenesis is more strongly associated with the generation of variant nef alleles than with env V3 variants, and that these arise by **CD8**+ T-cell pressure.

L34 ANSWER 68 OF 98 MEDLINE on STN
97289021. PubMed ID: 9143944. Structural constraints of **HIV**-1 Nef may curtail **escape** from HLA-B7-restricted **CTL** recognition. Bauer M; Lucchiari-Hartz M; Maier R; Haas G; Autran B; Eichmann K; Frank R; Maier B; Meyerhans A. (Abteilung Virologie, Universitat Freiburg, Germany.) Immunology letters, (1997 Feb) 55 (2) 119-22. Journal code: 7910006. ISSN: 0165-2478. Pub. country: Netherlands. Language: English.

L34 ANSWER 69 OF 98 MEDLINE on STN
97288738. PubMed ID: 9143689. **Escape** of **human immunodeficiency virus** from immune control. McMichael A J; Phillips R E. (Nuffield Department of Medicine, Institute of Molecular Medicine, John Radcliffe Hospital, Oxford, United Kingdom.. andrew.mcmichael%mailgate.jr2@ox.ac.uk) . Annual review of immunology, (1997) 15 271-96. Ref: 138. Journal code: 8309206. ISSN: 0732-0582. Pub. country: United States. Language: English.

AB **Cytotoxic T lymphocytes** (**CTL**) play a crucial role in the attempt to control infection with **human immunodeficiency virus** (**HIV**). Variation in epitopes recognized by **CTL** is common and frequently offers potential **escape** routes for mutant virus. Proof of **escape**, however, requires demonstration of increased frequency of virus particles or provirus that carry the **escape** sequence. There are now several recorded examples of virus variants that **escape** from **CTL** and are then selected. Most dramatic are those in which the **CTL** response has been dominated by **CTL** recognizing a single epitope that has suddenly changed, resulting in **escape** to fixation. This has been seen both early and late in the infection, leaving no doubt that **escape** occurs. Such **escape** is likely to be favored when the antiviral **CTL** response is oligoclonal and focused on a small number of immunodominant epitopes. The heterogeneous **CTL** response seen in many **HIV**-infected patients may result from successive waves of virus **escape** followed by new **CTL** responses specific for subdominant epitopes. Mutant virus can **escape** by several different routes, including failure of the mutated peptide to bind to the presenting HLA molecule and altered interactions with T cell receptors (TCR), including antagonism.

L34 ANSWER 70 OF 98 MEDLINE on STN
97236756. PubMed ID: 9079628. **HIV**-1 tat inhibits the 20 S proteasome and its 11 S regulator-mediated activation. Seeger M; Ferrell K; Frank R; Dubiel W. (Institute of Biochemistry, Humboldt-University, Medical Faculty (Charite), Monbijoustrasse 2A, 10117 Berlin, Germany.) Journal of biological chemistry, (1997 Mar 28) 272 (13) 8145-8. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB The proteasomal system consists of a proteolytic core, the 20 S proteasome, which associates in an ATP-dependent reaction with the 19 S regulatory complex to form the functional 26 S proteasome. In the absence of ATP, the 20 S proteasome forms a complex with the gamma-interferon-inducible 11 S regulator. Both the 20 S proteasome and the 11 S regulator have been implied in the generation of antigenic peptides. The **human immunodeficiency virus** (**HIV**)-1 Tat protein causes a number of different effects during acquired immunodeficiency syndrome (AIDS). Here we show that **HIV**-1 Tat protein strongly inhibits the peptidase activity of the 20 S proteasome and that it interferes with formation of the 20 S proteasome-11 S regulator complex. In addition, it slightly increases the activity of purified 26 S proteasome. These results may explain the mechanism by which **HIV**-1-infected cells **escape cytotoxic T lymphocyte** response and at least in part immunodeficiency in AIDS patients.

L34 ANSWER 71 OF 98 MEDLINE on STN
97203157. PubMed ID: 9050875. Positive selection of **HIV**-1 **cytotoxic T lymphocyte escape** variants during primary infection. Price D A; Goulder P J; Klenerman P; Sewell A K; Easterbrook P J; Troop M; Bangham C R; Phillips R E. (Nuffield Department of Clinical Medicine, John Radcliffe Hospital, Oxford, United Kingdom.) Proceedings of the National Academy of Sciences of the United States of America, (1997 Mar 4) 94 (5) 1890-5. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB **Cytotoxic T lymphocytes** (CTLs) are thought to play a crucial role in the termination of the acute primary **HIV**-1 syndrome, but clear evidence for this presumption has been lacking. Here we demonstrate positive selection of **HIV**-1 proviral sequences encoding variants within a **CTL** epitope in Nef, a gene product critical for viral pathogenicity, during and after seroconversion. These positively selected **HIV**-1 variants carried epitope sequence changes that either diminished or escaped **CTL** recognition. Other proviruses had mutations that abolished the Nef epitope altogether. These results provide clear evidence that CTLs exert selection pressure on the viral population in acute **HIV**-1 infection.

L34 ANSWER 72 OF 98 MEDLINE on STN
97185588. PubMed ID: 9033269. **HIV** is trapped and masked in the cytoplasm of lymph node follicular dendritic cells. Tacchetti C; Favre A; Moresco L; Meszaros P; Luzzi P; Truini M; Rizzo F; Grossi C E; Ciccone E. (Department of Human Anatomy, University of Genova, Italy.) American journal of pathology, (1997 Feb) 150 (2) 533-42. Journal code: 0370502. ISSN: 0002-9440. Pub. country: United States. Language: English.

AB To gain further insight into the pathogenesis of **human immunodeficiency virus** (**HIV**) infection, lymph nodes from seven asymptomatic **HIV**+ subjects were analyzed during the latent phase of disease. Both ultrastructural and immunohistochemical analyses revealed that, in all of the cases, plasma cells producing IgM/gamma were present in germinal centers. Secreted immunoglobulins formed extracellular deposits mimicking the follicular dendritic cell network. Immunoglobulin produced by germinal center plasma cells are specific for **HIV** because they bind the **HIV** env protein gp 120. Plasma cells producing antibodies with the same specificity were also abundant in the extrafollicular regions of lymph nodes. During the latent phase of infection, the virus largely accumulates within the germinal centers. Therefore, extracellular immunoglobulin may form immune complexes, as shown by the presence of **HIV**-specific antibodies, **HIV** particles, and complement components C3c, C3d, and C1q in the interdendritic spaces. When the ultrastructural localization of **HIV** in germinal centers was analyzed, abundant virus particles were found in the interdendritic spaces. In addition to this extracellular localization of **HIV**, receptor-mediated endocytosis of viral particles by follicular dendritic cells was observed. Complete **HIV** particles were found within the endosomal compartment of the follicular dendritic cells and, as complete viral particles, free in the cytoplasm, indicating that the virus may **escape** from the endocytic compartment. As the virus is abundant in the cytoplasm, this event leads to formation of a hidden reservoir within follicular dendritic cells. In this location, **HIV** escapes recognition by **cytotoxic T lymphocytes**. In contrast, virus budding indicating a productive infection of follicular dendritic cells that would render them susceptible to T-cell-mediated lysis has been seldom observed.

L34 ANSWER 73 OF 98 MEDLINE on STN
97170968. PubMed ID: 9018241. Late **escape** from an immunodominant **cytotoxic T-lymphocyte** response associated with progression to AIDS. Goulder P J; Phillips R E; Colbert R A; McAdam S; Ogg G; Nowak M A; Giangrande P; Luzzi G; Morgan B; Edwards A; McMichael A J; Rowland-Jones S. (Nuffield Department of Clinical Medicine, University of Oxford, UK.) Nature medicine, (1997 Feb) 3 (2) 212-7. Journal code: 9502015. ISSN: 1078-8956. Pub. country: United States. Language: English.

AB The precise role played by **HIV**-specific **cytotoxic T lymphocytes**

(CTL) in HIV infection remains controversial. Despite strong CTL responses being generated during the asymptomatic phase, the virus persists and AIDS ultimately develops. It has been argued that the virus is so variable, and the virus turnover so great that **escape** from **CTL** recognition would occur continually, but so far there is limited evidence for **CTL escape**. The opposing argument is that evidence for **CTL escape** is present but hard to find because multiple anti-**HIV** immune responses are acting simultaneously during the asymptomatic phase of infection. We describe six donors who make a strong **CTL** response to an immunodominant HLA-B27-restricted epitope. In the two donors who progressed to AIDS, **CTL escape** to fixation by the same mutation was observed, but only after 9-12 years of epitope stability. **CTL escape** may play an important role in the pathogenesis of **HIV** infection.

L34 ANSWER 74 OF 98 MEDLINE on STN
97151113. PubMed ID: 8995649. Overlapping epitopes in **human immunodeficiency virus** type 1 gp120 presented by HLA A, B, and C molecules: effects of viral variation on **cytotoxic T-lymphocyte** recognition. Wilson C C; Kalams S A; Wilkes B M; Ruhl D J; Gao F; Hahn B H; Hanson I C; Luzuriaga K; Wolinsky S; Koup R; Buchbinder S P; Johnson R P; Walker B D. (AIDS Research Center and Infectious Disease Unit, Massachusetts General Hospital, Boston 02114, USA.) Journal of virology, (1997 Feb) 71 (2) 1256-64. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB **Human immunodeficiency virus** (**HIV**)-specific **cytotoxic T lymphocytes** (**CTL**) are thought to exert immunologic selection pressure in infected persons, yet few data regarding the effects of this constraint on viral sequence variation in vivo, particularly in the highly variable Env protein, are available. In this study, **CD8+ HIV** type 1 (**HIV**-1) envelope-specific **CTL** clones specific for gp120 were isolated from peripheral blood mononuclear cells of four **HIV**-infected individuals, all of which recognized the same 25-amino-acid (aa) peptide (aa 371 to 395), which is partially contained in the CD4-binding domain of **HIV**-1 gp120. Fine mapping studies revealed that two of the clones optimally recognized the 9-aa sequence 375 to 383 (SFNCGGEFF), while the two other clones optimally recognized the epitope contained in the overlapping 9-aa sequence 376 to 384 (FNCGGEFFY). Lysis of target cells by the two clones recognizing aa 375 to 383 was restricted by HLA B15 and Cw4, respectively, whereas both clones recognizing aa 376 to 384 were restricted by HLA A29. Sequence variation, relative to the IIIB strain sequence used to identify **CTL** clones, was observed in autologous viruses in the epitope-containing region in all four subjects. However, poorly recognized autologous sequence variants were predominantly seen for the A29-restricted clones, whereas the clones specific for SFNCGGEFF continued to recognize the predominant autologous sequences. These results suggest that the HLA profile of an individual may not only be important in determining the specificity of **CTL** recognition but may also affect the ability to recognize virus variants and suppress **escape** from **CTL** recognition. These results also identify overlapping viral **CTL** epitopes which can be presented by HLA A, B, and C molecules.

L34 ANSWER 75 OF 98 MEDLINE on STN
97061054. PubMed ID: 8905100. Immunopathogenesis of **HIV** infection. Pantaleo G; Fauci A S. (Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Maryland 20892-1876, USA.) Annual review of microbiology, (1996) 50 825-54. Ref: 103. Journal code: 0372370. ISSN: 0066-4227. Pub. country: United States. Language: English.

AB The rate of progression of **HIV** disease may be substantially different among **HIV**-infected individuals. Following infection of the host with any virus, the delicate balance between virus replication and the immune response to the virus determines both the outcome of the infection, i.e. the persistence versus elimination of the virus, and the different rates of progression. During primary **HIV** infection, a burst of viremia occurs that disseminates virus to the lymphoid organs. A potent immune response ensues that substantially, but usually not completely, curtails virus

replication. This inability of the immune system to completely eliminate the virus leads to establishment of chronic, persistent infection that over time leads to profound immunosuppression. The potential mechanisms of virus **escape** from an otherwise effective immune response have been investigated. Clonal deletion of **HIV**-specific **cytotoxic T-cell** clones and sequestration of virus-specific cytotoxic cells away from the major site of virus replication represent important mechanisms of virus **escape** from the immune response that favor persistence of **HIV**. Qualitative differences in the primary immune response to **HIV** (i.e. mobilization of a restricted versus broader T-cell receptor repertoire) are associated with different rates of disease progression. Therefore, the initial interaction between the virus and immune system of the host is critical for the subsequent clinical outcome.

L34 ANSWER 76 OF 98 MEDLINE on STN
96228309. PubMed ID: 8642292. Inactivation of **human immunodeficiency virus** (**HIV**)-1 envelope-specific **CD8**+ **cytotoxic T lymphocytes** by free antigenic peptide: a self-veto mechanism?. Takahashi H; Nakagawa Y; Leggatt G R; Ishida Y; Saito T; Yokomuro K; Berzofsky J A. (Department of Microbiology and Immunology, Nippon Medical School, Tokyo, Japan.) Journal of experimental medicine, (1996 Mar 1) 183 (3) 879-89. Journal code: 2985109R. ISSN: 0022-1007. Pub. country: United States. Language: English.

AB Free peptide has been found to inhibit **cytotoxic T lymphocyte** (**CTL**) activity, and veto cells bearing peptide-major histocompatibility complex (MHC) complexes have been found to inactivate **CTL**, but the two phenomena have not been connected. Here we show that a common mechanism may apply to both. **CD8**+ **CTL** lines or clones specific for a determinant of the **human immunodeficiency virus** (**HIV**) 1 IIIB envelope protein gp160, P18IIIB, are inhibited by as little as 10 min exposure to the minimal 10-mer peptide, I-10, within P18IIIB, free in solution, in contrast to peptide already bound to antigen-presenting cells (APC), which does not inhibit. Several lines of evidence suggest that the peptide must be processed and presented by H-2Dd on the **CTL** itself to the specific T cell receptor (TCR) to be inhibitory. The inhibition was not killing, in that **CTL** did not kill 51Cr-labeled sister **CTL** in the presence of free peptide, and in mixing experiments with **CTL** lines of different specificities restricted by the same MHC molecule, Dd, the presence of free peptide recognized by one **CTL** line did not inhibit the activity of the other **CTL** line that could present the peptide. Also, partial recovery of activity could be elicited by restimulation with cell-bound peptide, supporting the conclusion that neither fratricide nor suicide (apoptosis) was involved. The classic veto phenomenon was ruled out by failure of peptide-bearing **CTL** to inactivate others. Using pairs of **CTL** lines of differing specificity but similar MHC restriction, each pulsed with the peptide for which the other is specific, we showed that the minimal requirement is simultaneous engagement of the TCR and class I MHC molecules of the same cell. This could occur in single cells or pairs of cells presenting peptide to each other. Thus, mechanistically, the inhibition is analogous to veto, and might be called self-veto. As a clue to a possible mechanism, we found that free I-10 peptide induced apparent downregulation of expression of specific TCR as well as interleukin 2 receptor, CD69, lymphocyte function-associated antigen 1, and **CD8**. This self-veto effect also has implications for in vivo immunization and mechanisms of viral **escape** from **CTL** immunity.

L34 ANSWER 77 OF 98 MEDLINE on STN
96180222. PubMed ID: 8786327. **Cytotoxic T lymphocytes** in asymptomatic long-term nonprogressing **HIV**-1 infection. Breadth and specificity of the response and relation to in vivo viral quasispecies in a person with prolonged infection and low viral load. Harrer T; Harrer E; Kalams S A; Barbosa P; Trocha A; Johnson R P; Elbeik T; Feinberg M B; Buchbinder S P; Walker B D. (AIDS Research Center and Infectious Disease Unit, Massachusetts General Hospital and Harvard Mmedical School, Boston, MA 02114, USA.) Journal of immunology (Baltimore, Md. : 1950), (1996 Apr 1) 156 (7) 2616-23. Journal code: 2985117R. ISSN: 0022-1767. Pub.

country. United States. Language: English.

AB Although vigorous activated and memory **CTL** have been associated with **HIV**-1 infection, data are lacking regarding the breadth of epitopes recognized in a given individual and the relationship to the viral quasispecies present in vivo. In this study we performed a detailed analysis of the **HIV**-1-specific **CTL** response in a seropositive person with documented **HIV**-1 infection of 15 yr duration, stable CD4 counts above 500 cells/ml, and viral load persistently below 500 molecules of RNA/ml of plasma. Epitope mapping studies revealed the presence of HLA class I-restricted **CTL** responses to six different epitopes in p17, p24, RT, Env, and Nef, which conferred broadly cross-reactive recognition of reported **HIV**-1 variants. Sequence analysis of autologous viruses revealed the absence of immune **escape** variants within five of the six epitopes. Despite consistently low viral RNA levels in plasma and viral DNA levels in PBMC, in vivo-activated circulating **CTL** were detected against three of the epitopes. Five of the six epitopes, including the three dominant epitopes, have been detected in persons with progressive disease, suggesting that nonprogressors may not target unique epitopes. This study demonstrates that **HIV**-1-specific **CTL** can be highly activated and broadly directed in the setting of an extremely low viral load, and that neither high viral load nor antigenic diversity is required for the generation of a multispecific **CTL** response. Although the detection of strong **CTL** responses, low viral load, and lack of immune **escape** are consistent with the hypothesis that **CTL** may contribute to lack of disease progression in this individual, the contribution of these responses to maintenance of the asymptomatic state remains to be determined.

L34 ANSWER 78 OF 98 MEDLINE on STN

96173871. PubMed ID: 8599886. Serum cytokine profiles in acute primary **HIV**-1 infection and in infectious mononucleosis. Biglino A; Sinicco A; Forno B; Pollono A M; Sciandra M; Martini C; Pich P; Gioannini P. (Institute of Infectious Disease, University of Turin, Italy.) Clinical immunology and immunopathology, (1996 Jan) 78 (1) 61-9. Journal code: 0356637. ISSN: 0090-1229. Pub. country: United States. Language: English.

AB Serum cytokine profiles, T-cell subsets, and general parameters of immune activation were evaluated in 15 patients with acute primary **HIV**-1 infection, and compared with those obtained from 18 patients with acute primary Epstein-Barr virus (EBV) infection and from 18 control subjects in order to elucidate possible defects of immune response to **HIV** in early phases of virus-host interaction. Mean CD4+ cell count, serum concentrations of interleukin (IL)-2, IL-4, soluble IL-2 receptor (sIL-2R), tumor necrosis factor (TNF)-alpha, 5'-neopterin, and beta 2-microglobulin were significantly lower in acute **HIV**-1 infection than in EBV infection. Both acute **HIV**-1 and EBV infections were characterized by significantly higher mean **CD8**+ cell count and soluble **CD8** antigen (sCD8) levels compared to control subjects, while acute **HIV**-1 infection was accompanied by the highest interferon (IFN)-gamma serum concentrations. In primary **HIV**-1 infection, significant impairment of CD4+- mediated T-helper function may lead to viral **escape** and persistence of infection despite an early and vigorous **CD8**+ T-lymphocyte activation.

L34 ANSWER 79 OF 98 MEDLINE on STN

96085065. PubMed ID: 7481824. **Cytotoxic T lymphocyte** lysis inhibited by viable **HIV** mutants. Meier U C; Klenerman P; Griffin P; James W; Koppe B; Larder B; McMichael A; Phillips R. (Nuffield Department of Clinical Medicine, John Radcliffe Hospital, Headington, Oxford, UK.) Science, (1995 Nov 24) 270 (5240) 1360-2. Journal code: 0404511. ISSN: 0036-8075. Pub. country: United States. Language: English.

AB Immune **evasion** by the **human immunodeficiency virus** (**HIV**) is unexplained but may involve the mutation of viral antigens. When **cytotoxic T lymphocytes** engaged CD4-positive cells that were acutely infected with **HIV** bearing natural variant epitopes in reverse transcriptase, substantial inhibition of specific antiviral lysis was observed. Mutant viruses capable of these transactive effects could

facilitate the persistence of a broad range of **HIV** variants in the face of an active and specific immune response.

L34 ANSWER 80 OF 98 MEDLINE on STN

96030939. PubMed ID: 7475080. Immune responses against multiple epitopes. Nowak M A; May R M; Sigmund K. (Department of Zoology, University of Oxford, U.K.) Journal of theoretical biology, (1995 Aug 7) 175 (3) 325-53. Journal code: 0376342. ISSN: 0022-5193. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The current understanding of antigenic **escape** dynamics is based on models with single epitopes. The usual idea is that a mutation which enables a pathogen (virus, bacteria, etc) to **escape** from a given immune response confers a selective advantage. The "**escape** mutant" may then increase in abundance until it induces a new specific response against itself. In this paper a new picture is developed, based on mathematical models of immune responses against several epitopes; the simplest such models can have very complicated dynamics, with some surprising features. The emergence of an **escape** mutant can shift the immunodominant response to another epitope. Even in the absence of mutations, antigenic oscillation is found, with distinct peaks of different virus variants and fluctuations in the size and specificity of the immune responses. The model also provides a general theory for immunodominance in the presence of antigenic variation. Immunodominance is determined by the immunogenicity and by the antigenic diversity of the competing epitopes. Antigenic oscillations and fluctuations in the **cytotoxic T-lymphocyte** response have been observed in infections with the **human immunodeficiency virus** (**HIV**). Shifting the immune responses to weaker epitopes can represent a mechanism for disease progression based on evolutionary dynamics and antigenic diversity of the virus.

L34 ANSWER 81 OF 98 MEDLINE on STN

96013809. PubMed ID: 7474126. Persistent infection of macaques with simian-human immunodeficiency viruses. Li J T; Halloran M; Lord C I; Watson A; Ranchalis J; Fung M; Letvin N L; Sodroski J G. (Dana-Farber Cancer Institute, Department of Pathology, Harvard Medical School, Boston, Massachusetts, USA.) Journal of virology, (1995 Nov) 69 (11) 7061-7. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Chimeric simian-human immunodeficiency viruses (SHIV) containing the **human immunodeficiency virus** type 1 (**HIV**-1) tat, rev, env, and, in some cases, vpu genes were inoculated into eight cynomolgus monkeys. Viruses could be consistently recovered from the **CD8**-depleted peripheral blood lymphocytes of all eight animals for at least 2 months. After this time, virus isolation varied among the animals, with viruses continuing to be isolated from some animals beyond 600 days after inoculation. The level of viral RNA in plasma during acute infection and the frequency of virus isolation after the initial 2-month period were higher for the Vpu-positive viruses. All of the animals remained clinically healthy, and the absolute numbers of CD4-positive lymphocytes were stable. Antibodies capable of neutralizing **HIV**-1 were generated at high titers in animals exhibiting the greatest consistency of virus isolation. Strain-specific **HIV**-1-neutralizing antibodies were initially elicited, and then more broadly neutralizing antibodies were elicited. env sequences from two viruses isolated more than a year after infection were analyzed. In the Vpu-negative SHIV, for which virus loads were lower, a small amount of env variation, which did not correspond to that found in natural **HIV**-1 variants, was observed. By contrast, in the Vpu-positive virus, which was consistently isolated from the host animal, extensive variation of the envelope glycoproteins in the defined variable gp120 regions was observed. **Escape** from neutralization by CD4 binding site monoclonal antibodies was observed for the viruses with the latter envelope glycoproteins, and the mechanism of **escape** appears to involve decreased binding of the antibody to the monomeric gp120 glycoproteins. The consistency with which SHIV infection of cynomolgus monkeys is initiated and the similarities in the neutralizing antibody response to SHIV and **HIV**-1 support the utility of this model system for the study of **HIV**-1 prophylaxis.

L34 ANSWER 82 OF 98 MEDLINE on STN

95347391. PubMed ID: 7542596. The effects of natural altered peptide ligands on the whole blood **cytotoxic T lymphocyte** response to **human immunodeficiency virus**. Klenerman P; Meier U C; Phillips R E; McMichael A J. (Nuffield Department of Clinical Medicine, John Radcliffe Hospital, Oxford, GB.) European journal of immunology, (1995 Jul) 25 (7) 1927-31. Journal code: 1273201. ISSN: 0014-2980. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB **Cytotoxic T lymphocytes** (**CTL**) directed against **human immunodeficiency virus** (**HIV**)-1 are detectable in the majority of infected individuals, and their early appearance as the initial viremia is suppressed is thought to represent a potent antiviral response. Variation which arises in **CTL** epitopes can affect recognition by **CTL**, and we have observed previously that variant epitopes in **HIV**-1 gag which arise in **HIV**-1-seropositive donors may act as T cell receptor (TCR) antagonists of their own **CTL** (Klenerman et al., Nature 1994, 369: 403). The most important question arising from these observations is the extent of these immune **escape** mechanisms in vivo. Here we show that fresh, uncultured lymphocytes taken directly from **HIV**-1-infected patients are susceptible to TCR antagonism by variants present within their own virus. In contrast to HLA Class II-restricted T cell responses, where anergy may be induced, we find that in vitro, natural variants may stimulate and sustain growth of **CTL**. These **CTL** lines retain lytic specificity exclusively for the original peptide. If this represents events in vivo, natural **HIV** altered peptide ligands (APL) have the capacity to inhibit the range of **CTL** directed against an epitope, not simply those clones selected in vitro. Partial activation of **CTL** by APL could also act to drive an ineffectual **CTL** response incapable of lysing infected cells bearing these natural antigenic variants. Distortion of lymphocyte populations and function by APL might represent a further mechanism of immune **evasion** by **HIV**.

L34 ANSWER 83 OF 98 MEDLINE on STN

95220421. PubMed ID: 7705402. HLA-dependent variations in **human immunodeficiency virus** Nef protein alter peptide/HLA binding. Couillin I; Connan F; Culmann-Penciolelli B; Gomard E; Guillet J G; Choppin J. (Unite 152, Institut National de la Sante et de la Recherche Medicale, Institut Cochin de Genetique, Moleculaire, Paris, France.) European journal of immunology, (1995 Mar) 25 (3) 728-32. Journal code: 1273201. ISSN: 0014-2980. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB In **human immunodeficiency virus** (**HIV**) infection, sequence variations within defined **cytotoxic T lymphocyte** (**CTL**) epitopes may lead to **escape** from **CTL** recognition. In a previous report, we have shown that the variable central region of **HIV** Nef protein (amino acids 73-144) that contains potential **CTL** epitopes, can **escape** the **CTL** response. We suggested that this non recognition occurs through a variety of mechanisms. In particular, we provided evidence that **HIV** Nef sequences recovered from HLA-A11-expressing individuals have alterations in the major anchor residues essential for binding of the two Nef epitopes (amino acids 73-82 and 84-92) to the HLA-A11 molecule. Here, we investigate in more detail whether variations in autologous Nef sequences affect HLA binding, leading to **CTL escape**. Potential epitopes were sought by testing Nef peptides containing the HLA-A11-specific motif or related motifs. We confirmed that only the two previously described epitopes identified in cytolysis tests have optimal reactivity with the HLA-A11 molecule. We then sequenced several viral variants from donors that do not express the HLA-A11 molecule and compared the variability of these epitopes with those obtained from HLA-A11-expressing individuals. One substitution (Leu85) found in the sequences isolated from both populations increase the reactivity of the HLA-A11-restricted epitope 84-92, and might explain the difference in immunogenicity observed between the two HLA-A11-restricted epitopes from HLA-A11+ individuals. In addition, selective variations were only detected in virus isolated from HLA-A11-expressing individuals. Furthermore, examination of the

association of variant peptides with the HLA A11 molecule demonstrated
that a single substitution within the minimal epitope could not always completely abrogate HLA binding, suggesting that multiple alterations within a particular epitope may accumulate during disease progression, allowing the virus to **escape** **CTL** recognition.

L34 ANSWER 84 OF 98 MEDLINE on STN
95173425. PubMed ID: 7868892. Sequence constraints and recognition by **CTL** of an HLA-B27-restricted **HIV**-1 gag epitope. Nietfield W; Bauer M; Fevrier M; Maier R; Holzwarth B; Frank R; Maier B; Riviere Y; Meyerhans A. (Department of Virology, University of Freiburg, Germany.) Journal of immunology (Baltimore, Md. : 1950), (1995 Mar 1) 154 (5) 2189-97. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB Previous studies on the variation of an immunodominant HLA-B27-restricted **HIV**-1 gag p24 epitope (KRWIIL GLNK, amino acids 263-272) have demonstrated the persistence of variants recognized by **CTL**. Sequence comparisons of **HIV** isolates showed that this region is relatively conserved and as a consequence might restrict antigenic variation. To evaluate the possibility of **HIV**-1 to yield infectious mutants of this epitope that lack the ability to bind to HLA-B27 or **escape** HLA-B27-restricted **CTL** recognition, single-point mutations were constructed in the infectious molecular clone of **HIV**-1 Lai. Changes of arginine 264, the anchor amino acid for HLA-B27, to lysine or glycine resulted in infectious **HIV**-1 variants. The respective synthetic peptides showed reduced ability to sensitize target cells for **CTL** recognition and a corresponding loss of binding affinity to HLA-B27. In contrast, mutation of glycine 269 to lysine or glutamate abrogated **HIV**-1 infectivity. The corresponding peptides were able to bind to HLA-B27 but were not recognized by **CTL**. These data show that **HIV**-1 tolerates some genetic variation of the HLA-B27-restricted **CTL** epitope in gag p24 and that single-point mutations can alter quantitatively the immunologic properties. Further, it demonstrates that the mere nonrecognition of peptides derived from quasispecies analysis of small regions might simply correspond to nonviable virus variants and cannot be taken as evidence for **CTL** **escape** mutants. Together with the previously published data on the persistence of **CTL** epitopes, these results suggest that **CTL** do not play a major role in driving **HIV**-1 evolution in vivo.

L34 ANSWER 85 OF 98 MEDLINE on STN
95008914. PubMed ID: 7523031. Envelope sequence variation, neutralizing antibodies, and primate lentivirus persistence. Burns D P; Desrosiers R C. (New England Regional Primate Research Center, Harvard Medical School, Southborough, MA 01772-9102.) Current topics in microbiology and immunology, (1994) 188 185-219. Ref: 174. Journal code: 0110513. ISSN: 0070-217X. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB Studies in ungulate lentivirus systems clearly indicate that neutralization **escape** variants emerge over time in chronically infected animals. Studies in the EIAV system, in particular, have provided strong evidence that the humoral branch of the immune system is at least one selective force acting on an array of viral variants. In previous studies with the ungulate lentiviruses, molecularly cloned virus was never used, and plaque-purified virus was only sometimes used; the genetic determinants responsible for antigenic variation and immune selection were not determined. While molecular clones are available for **HIV**-1, immune selection studies have been hampered in this system by the fact that **HIV**-1 is infectious only for chimpanzees, which do not develop disease and are available in only limited numbers. Experiments on immune selection in humans are generally complicated by lack of knowledge on the time of infection and the genetic make-up of the infecting virus. Our studies on SIV immune selection summarized in this review provide definitive evidence that neutralization-resistant variants emerge in an individual during persistent infection by primate lentiviruses. By cloning viral envelope genes from rhesus monkeys over time and obtaining sequential serum samples from them, we have been able to study not only

the evolution of envelope sequences but also the emergence of neutralization-resistant variants. Reciprocal neutralization studies were performed using parental and variant specific sera, and immune selection was demonstrated using molecularly cloned virus of defined sequence. During the course of persistent infection with SIV and **HIV**, there is clear selective pressure for change in discrete variable regions of envelope. The host neutralizing antibody response appears to be at least one of the selective forces driving sequence change in envelope since one result of the sequence variation is the emergence of neutralization **escape** mutants. This indicates that neutralizing antibodies do serve to limit **HIV** and SIV replication during the lengthy asymptomatic stage of infection. The coincidence of neutralization domains of **HIV** and/or SIV with variable regions V1, V2, V3, V4, V5, and V6 suggests a direct relationship between neutralization domains and the emergence of sequence variants. However, different selective forces may be responsible all or in part for driving sequence changes in some variable domains (summarized in Table 2). For example, alterations in cell and/or tissue tropism may be responsible at least in part for driving change in V3 and the **cytotoxic T-lymphocyte** response may be responsible for driving change in the signal peptide (V0; Henderson et al. 1992; Wei and Cresswell 1992).(ABSTRACT TRUNCATED AT 400 WORDS)

L34 ANSWER 86 OF 98 MEDLINE on STN
94342838. PubMed ID: 7520471. Virus **escape** from **CTL** recognition. Koup R A. (Aaron Diamond AIDS Research Center, Department of Medicine, New York University School of Medicine, New York 10016.) Journal of experimental medicine, (1994 Sep 1) 180 (3) 779-82. Journal code: 2985109R. ISSN: 0022-1007. Pub. country: United States. Language: English.

L34 ANSWER 87 OF 98 MEDLINE on STN
94303221. PubMed ID: 8030265. Functional consequences of mutations in **HIV**-1 Gag p55 selected by **CTL** pressure. Zhang W H; Hockley D J; Nermut M V; Jones I M. (NERC Institute of Virology, Oxford, United Kingdom.) Virology, (1994 Aug 15) 203 (1) 101-5. Journal code: 0110674. ISSN: 0042-6822. Pub. country: United States. Language: English.

AB Amino acid changes in the CA domain of the p55 Gag protein of **HIV**-1 have been observed during the course of an infection that appear to correlate with **escape** from **cytotoxic T cell** surveillance (Phillips et al., Nature 354, 453-459, 1991). A corollary of this observation is that all such changes should be functionally silent but, as the changes were observed in populations of virus, this has not been formally demonstrated. We have introduced the amino acid changes representative of those observed to occur in vivo into the Gag p55 gene cloned in the baculovirus expression system where the wild-type gene product produces virus-like particles (VLP). We show that none of these mutations affect particle formation as judged by VLP morphology and density despite their location within a sequence of the Gag open reading frame known to be important for assembly. These data add tacit support to the hypothesis that **CTL** pressure can drive virus evolution in **HIV** and add to the fine mapping of sequences involved in Gag subunit interactions.

L34 ANSWER 88 OF 98 MEDLINE on STN
94194282. PubMed ID: 8145043. Longitudinal analysis of T cell receptor (TCR) gene usage by **human immunodeficiency virus** 1 envelope-specific **cytotoxic T lymphocyte** clones reveals a limited TCR repertoire. Kalams S A; Johnson R P; Trocha A K; Dynan M J; Ngo H S; D'Aquila R T; Kurnick J T; Walker B D. (Infectious Disease Unit, Massachusetts General Hospital, Boston.) Journal of experimental medicine, (1994 Apr 1) 179 (4) 1261-71. Journal code: 2985109R. ISSN: 0022-1007. Pub. country: United States. Language: English.

AB **Human immunodeficiency virus** 1 (**HIV**-1) infection is associated with a vigorous cellular immune response that allows detection of **cytotoxic T lymphocyte** (**CTL**) activity using freshly isolated peripheral blood mononuclear cells (PBMC). Although restricting class I antigens and epitopes recognized by **HIV**-1-specific **CTL** have been defined, the effector cells mediating this vigorous response have been

characterized less well. Specifically, no studies have addressed the breadth and duration of response to a defined epitope. In the present study, a longitudinal analysis of T cell receptor (TCR) gene usage by **CTL** clones was performed in a seropositive person using TCR gene sequences as a means of tracking responses to a well-defined epitope in the glycoprotein 41 transmembrane protein. 10 **CTL** clones specific for this human histocompatibility leukocyte antigen-B14-restricted epitope were isolated at multiple time points over a 31-mo period. All clones were derived from a single asymptomatic **HIV**-1-infected individual with a vigorous response to this epitope that was detectable using unstimulated PBMC. Polymerase chain reaction amplification using V alpha and V beta family-specific primers was performed on each clone, followed by DNA sequencing of the V-D-J regions. All 10 clones utilized V alpha 14 and V beta 4 genes. Sequence analysis of the TCR revealed the first nine clones isolated to also be identical at the nucleotide level. The TCR-alpha junctional region sequence of the tenth clone was identical to the junctional region sequences of the other nine, but this clone utilized distinct D beta and J beta gene segments. This study provides evidence that the observed high degree of **HIV**-1-specific **CTL** activity may be due to monoclonal or oligoclonal expansion of specific effector cells, and that progeny of a particular **CTL** clone may persist for prolonged periods in vivo in the presence of a chronic productive viral infection. The observed limited TCR diversity against an immunodominant epitope may limit recognition of virus variants with mutations in regions interacting with the TCR, thereby facilitating immune **escape**.

L34 ANSWER 89 OF 98 MEDLINE on STN

93353592. PubMed ID: 8394444. Early events in immune **evasion** by the lentivirus maedi-visna occurring within infected lymphoid tissue. Bird P; Blacklaws B; Reyburn H T; Allen D; Hopkins J; Sargan D; McConnell I. (Department of Veterinary Pathology, University of Edinburgh, Summerhall, Scotland.) Journal of virology, (1993 Sep) 67 (9) 5187-97. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Infections caused by lentiviruses, including **human immunodeficiency virus**, are characterized by slowly progressive disease in the presence of a virus-specific immune response. The earliest events in the virus-host interaction are likely to be important in determining disease establishment and progression, and the kinetics of these early events following lentiviral infection are described here. Lymphatic cannulation in the sheep has been used to monitor both the virus and the immune response in efferent lymph after infection of the node with maedi-visna virus (MVV). Viral replication and dissemination could be detected and consisted of a wave of MVV-infected cells leaving the node around 9 to 18 days postinfection. No cell-free virus was recovered despite the fact that soluble MVV p25 was detected in lymph plasma. The maximum frequency of MVV-infected cells was only 11 in 10(6) but over the first 20 days of infection amounted to greater than 10(4) virus-infected cells leaving the node. There was a profound increase in the output of activated lymphoblast from the lymph nodes of infected sheep, characterized by an increased percentage of **CD8**+ lymphoblasts. All of the **CD8**+ lymphoblasts at the peak of the response expressed both major histocompatibility complex class II DR and DQ molecules but not interleukin-2 receptor (CD25). The in vitro proliferative response of efferent lymph cells existing the node after challenge with MVV to both recombinant human interleukin-2 and the mitogen concanavalin A was decreased between days 8 and 16 postinfection, and a specific proliferative response to MVV was not detected until after day 15. Despite the high level of **CD8+** lymphoblasts in efferent lymph, direct MVV-specific cytotoxic activity was demonstrated in only one of the five MVV-challenged sheep. MVV-specific antibody responses, including neutralization and MVV p25 immune complexes in efferent lymph, were detectable during the major period of virus dissemination. The relationship of these findings to the **evasion** of the host's acute immune response by MVV is discussed.

L34 ANSWER 90 OF 98 MEDLINE on STN

93199008. PubMed ID: 7688087. How does the **HIV escape cytotoxic T**
cell immunity?. Phillips R E; McMichael A J. (Institute of Molecular Medicine, John Radcliffe Hospital, Headington, Oxford, UK.) Chemical immunology, (1993) 56 150-64. Ref: 74. Journal code: 9001090. ISSN: 1015-0145. Pub. country: Switzerland. Language: English.

L34 ANSWER 91 OF 98 MEDLINE on STN
93103809. PubMed ID: 1466955. **Human immunodeficiency virus** variants that **escape cytotoxic T-cell** recognition. Rowland-Jones S L; Phillips R E; Nixon D F; Gotch F M; Edwards J P; Ogunlesi A O; Elvin J G; Rothbard J A; Bangham C R; Rizza C R; +. (Institute of Molecular Medicine, John Radcliffe Hospital, Headington, Oxford, England.) AIDS research and human retroviruses, (1992 Aug) 8 (8) 1353-4. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

L34 ANSWER 92 OF 98 MEDLINE on STN
93100827. PubMed ID: 7677956. Recognition of a highly conserved region of **human immunodeficiency virus** type 1 gp120 by an HLA-Cw4-restricted **cytotoxic T-lymphocyte** clone. Johnson R P; Trocha A; Buchanan T M; Walker B D. (Infectious Disease Unit, Massachusetts General Hospital, Boston 02114.) Journal of virology, (1993 Jan) 67 (1) 438-45. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB **Human immunodeficiency virus** type 1 (**HIV**-1) isolates exhibit extensive sequence variation, particularly in the gp120 subunit of the envelope glycoprotein, and the degree of this variation has raised questions as to whether conserved regions of the **HIV**-1 envelope can be recognized by the host immune response. A **CD8+ cytotoxic T-lymphocyte** (**CTL**) clone specific for the **HIV**-1 envelope was derived by culturing peripheral blood mononuclear cells from an **HIV**-1 seropositive subject in the presence of a CD3-specific monoclonal antibody, interleukin-2, and irradiated allogeneic peripheral blood mononuclear cells. Lysis of target cells was restricted by an HLA-C molecule, Cw4, which has not been previously shown to present viral antigen to **CTL**. Mapping of the specificity of this **CTL** clone by using synthetic **HIV**-1 peptides localized the epitope to an 8-amino-acid region of gp120 (amino acids 376 to 383) which is conserved among approximately 90% of sequenced viral isolates. Examination of the recognition of variant peptides by this **CTL** clone demonstrated that a single, nonconservative amino acid substitution within the 8-amino-acid minimal epitope could abrogate lysis of targets incubated with the variant peptide. The identification of a **CTL** epitope in a highly conserved region of gp120 documents the ability of cellular immune responses of infected persons to respond to relatively invariant portions of this highly variable envelope glycoprotein. However, the ability of even a single-amino-acid change in gp120 to abolish lysis by **CTL** supports the hypothesis that sequence variation in **HIV**-1 may serve as a mechanism of immune **escape**. In addition, the identification of an HLA-C molecule presenting viral antigen to **CTL** supports a functional role for these molecules.

L34 ANSWER 93 OF 98 MEDLINE on STN
93094606. PubMed ID: 1460291. **Cytotoxic T lymphocytes** do not appear to select for mutations in an immunodominant epitope of simian immunodeficiency virus gag. Chen Z W; Shen L; Miller M D; Ghim S H; Hughes A L; Letvin N L. (Harvard Medical School, New England Regional Primate Research Center, Southborough, MA 01772.) Journal of immunology (Baltimore, Md. : 1950), (1992 Dec 15) 149 (12) 4060-6. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB Studies to date assessing **HIV escape** from **CTL** in vivo have yielded conflicting results. Previous studies have demonstrated that simian immunodeficiency virus of macaques (SIVmac)-infected rhesus monkeys expressing the MHC class I allele Mamu-A*01 reproducibly develop a gag-specific **CTL** response limited to a 9-amino acid epitope of the SIVmac gag protein (residues 182-190 within peptide 11C). To determine whether **CTL** have a role in selecting for AIDS virus mutants, we examined

mutations in SIVmac proviral DNA encoding this gag CTL epitope in PBL of infected rhesus monkeys. Three Mamu-A*01+ rhesus monkeys were infected with SIVmac and assessed for gag- and peptide 11C-specific **CTL** responses. This specific **CTL** response was maintained in two monkeys, but lost in the third animal 2 yr after infection. The generation of proviral gag mutations was then determined by sequencing 500-bp proviral fragments amplified from fresh PBL obtained from the monkeys more than 2.5 yr after infection. Although numerous point mutations were characterized in 131 polymerase chain reaction-generated clones of SIVmac gag, only four mutations within the gag **CTL** epitope-coding region of the genome were identified. Comparison of synonymous and nonsynonymous nucleotide substitutions in the regions encoding peptide 11C (p11C) and the flanking gag protein indicated a lack of selective pressure for viral mutations in the **CTL** epitope coding region. Interestingly, a predominant gag mutant encoding a single amino acid change in p11C was found in a monkey which lost its **CTL** activity. However, even in this setting there was no evidence for selection of mutations in the **CTL** epitope coding region when compared with the flanking region. Furthermore, synthetic peptides corresponding to all naturally occurring variants in the gag epitope-coding region were recognized by cloned and bulk cultured effector cells of the infected monkeys with persistent **CTL**. These results indicate that SIVmac gag- and p11C-specific **CTL** do not select for mutations in the immunodominant epitope-coding region and that the naturally occurring mutants do not appear to **escape** **CTL** recognition.

L34 ANSWER 94 OF 98 MEDLINE on STN
92086044. PubMed ID: 1721107. **Human immunodeficiency virus** genetic variation that can **escape cytotoxic T cell** recognition. Phillips R E; Rowland-Jones S; Nixon D F; Gotch F M; Edwards J P; Ogunlesi A O; Elvin J G; Rothbard J A; Bangham C R; Rizza C R; +. (Molecular Immunology Group, Institute of Molecular Medicine, University of Oxford, John Radcliffe Hospital, UK.) Nature, (1991 Dec 12) 354 (6353) 453-9. Journal code: 0410462. ISSN: 0028-0836. Pub. country: ENGLAND: United Kingdom. Language: English.

AB In a longitudinal study of **HIV** seropositive patients, there were fluctuations in the specificity of **cytotoxic T cells** for the virus. This was matched by variability in proviral gag DNA epitope sequences in the lymphocytes of these patients. Some of these viral variants are not recognized by autologous T cells. Accumulation of such mutations in T-cell antigenic targets would provide a mechanism for immune **escape**.

L34 ANSWER 95 OF 98 MEDLINE on STN
92008181. PubMed ID: 1717289. In vivo persistence of a **HIV**-1-encoded HLA-B27-restricted **cytotoxic T lymphocyte** epitope despite specific in vitro reactivity. Meyerhans A; Dadaglio G; Vartanian J P; Langlade-Demoyen P; Frank R; Asjo B; Plata F; Wain-Hobson S. (Laboratoire de Retrovirologie Moleculaire, Institut Pasteur, Paris, France.) European journal of immunology, (1991 Oct) 21 (10) 2637-40. Journal code: 1273201. ISSN: 0014-2980. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB A large number of **human immunodeficiency virus** type 1 (**HIV**-1) specific HLA-restricted **cytotoxic T cell** (**CTL**) epitopes have been mapped, including an HLA-B27-restricted immunodominant epitope within p25gag. Accordingly, this segment of the **HIV**-1 provirus was amplified by the polymerase chain reaction from DNA derived from fresh uncultured peripheral blood mononuclear cells (PBMC) of four HLA-B27 **HIV**-1-infected individuals. In all cases the majority of infected PBMC bore sequences encoding the HLA-B27-restricted peptide. **CTL escape** mutants had not accumulated in vivo 8 and 14 months later despite demonstrable **CTL** activity in vitro. These data emphasize the importance of silently infected lymphocytes in evading immune surveillance.

L34 ANSWER 96 OF 98 MEDLINE on STN
90348962. PubMed ID: 1696684. Viral **escape** by selection of **cytotoxic T cell**-resistant virus variants in vivo. Pircher H; Moskophidis D; Rohrer U; Burki K; Hengartner H; Zinkernagel R M. (Institute of Pathology,

University Hospital, Zurich, Switzerland.) Nature, (1990 Aug 16) 346 (6285) 629-33. Journal code: 0410462. ISSN: 0028-0836. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Viruses persist in an immune population, as in the case of influenza, or in an individual, as postulated for **human immunodeficiency virus**, when they are able to **escape** existent neutralizing antibody responses by changing their antigens. It is now shown that viruses can in principle **escape** the immunosurveillance of virus-specific **cytotoxic T cells** by mutations that alter the relevant T-cell epitope.

L34 ANSWER 97 OF 98 MEDLINE on STN

90234249. PubMed ID: 2561343. Immunopathology of lentiviral infections in ungulate animals. Narayan O. (Johns Hopkins University School of Medicine, Division of Comparative Medicine, Baltimore, Maryland.) Current opinion in immunology, (1989-90 Feb) 2 (3) 399-402. Ref: 17. Journal code: 8900118. ISSN: 0952-7915. Pub. country: United States. Language: English.

AB The immunopathogenesis of lentiviral lesions in sheep and goats requires continuous replication of the virus in tissues of the animal. This entails **escape** from various defense mechanisms of the host. Viral expression occurs mainly in tissue-specific macrophage populations and viral proteins produced by the cells induce and combine with antibodies to form immune complexes. These may be pathogenic locally. Infected macrophages also present lentiviral antigens to T lymphocytes and this results in a cascade of cellular responses including proliferation and accumulation of **CD8** cells. Cytokines including interferon(s) are produced by lymphocytes and these enhance the antigen-presenting capacity of the macrophages. These lymphoproliferative cellular responses vary from those in **human immunodeficiency virus**- and simian immunodeficiency virus-infected hosts, mainly because CD4 cells of sheep and goats are not killed by the viruses. These cells, therefore, respond immunologically to viral antigens and this leads to active-chronic inflammation.

L34 ANSWER 98 OF 98 MEDLINE on STN

90063467. PubMed ID: 2479705. Structural requirements for class I MHC molecule-mediated antigen presentation and **cytotoxic T cell** recognition of an immunodominant determinant of the **human immunodeficiency virus** envelope protein. Takahashi H; Houghten R; Putney S D; Margulies D H; Moss B; Germain R N; Berzofsky J A. (Molecular Immunogenetics and Vaccine Research Section, National Cancer Institute, Bethesda, Maryland 20892.) Journal of experimental medicine, (1989 Dec 1) 170 (6) 2023-35. Journal code: 2985109R. ISSN: 0022-1007. Pub. country: United States. Language: English.

AB In H-2d mice, the immunodominant determinant of the **HIV**-1-IIIB gp160 envelope glycoprotein recognized by **CD8**+ **CTL** is represented by a 15-residue synthetic peptide (315-329: RIQRGPGRAFVTIGK). This peptide is seen in association with the Dd class I MHC molecule expressed on H-2k L cell fibroblast targets. We explored the structural requirements for **CTL** recognition of this peptide at the levels of both the peptide molecule and the class I MHC molecule. Using several transfectants expressing recombinant Dd/Ld molecules, we found that presentation of this epitope required both the alpha 1 and alpha 2 domains of the Dd molecule, in contrast to certain instances of allorecognition for which alpha 1 of Dd was sufficient in association with alpha 2 of Ld. Because this peptide derives from a hypervariable segment of the **HIV** envelope, substituted peptides could be used to define not only the structures affecting interaction of peptide with class I MHC molecule and with the TCR, but also the structural basis for the effect of naturally occurring viral variation on **CTL** recognition. The **CTL**-LINE specific for this **HIV**-1-IIIB-derived sequence could not recognize the **HIV**-1-RF variant-derived sequence from exactly the same site (315-329:--HIGPGRVIYATGQ). Peptides with single amino acid substitutions from the **HIV**-1-IIIB sequence toward the **HIV**-1-RF sequence were made to test the effect of each residue significantly affected recognition, and only one, 324(F), was obligatory. Moreover, both 322(R) and 324(F) substituted peptides failed to inhibit the binding of the wild type peptide to the MHC

molecule. Therefore, the amino acids 322(K) and 324(I) seem to be involved in regulating peptide interaction with the Dd class I MHC molecule. In contrast, 325(V) appeared to affect interaction with the TCR. We suggest that sequence variations among known **HIV**-1 isolates that affect peptide binding to MHC such as those described here, if occurring during the course of infection of an individual, could result in failure of the MHC molecules of that individual to present the peptide. If the number of dominant **HIV CTL** epitopes is indeed very limited, such a blind spot could allow the virus to **escape** immune control, proliferate rapidly, and cause AIDS.

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=> d his

     (FILE 'HOME' ENTERED AT 19:42:02 ON 01 APR 2004)

     FILE 'USPATFULL' ENTERED AT 19:42:32 ON 01 APR 2004
                E FRANCHINI GENOVEFFA/IN
L1            7 S E3
L2            0 S ZDENEK HEL/IN
                E ZDENEK HEL/IN
L3            0 S HEL ZDENEK/IN S HEL ZDENEK/IN
L4            0 S GENE SHEARER/IN
L5            1 S SHEARER GENE/IN
                E SHEARER GENE/IN
L6            7 S E4
                E NACSA JANOS/IN

     FILE 'MEDLINE' ENTERED AT 19:47:38 ON 01 APR 2004
                E FRANCHINI G/AU
L7          196 S E3 OR E4
L8           67 S L7 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L9           16 S L8 AND (MHC OR MAJOR HISTOCOMPATIBILITY OR CTL OR CYTOTOXIC T
L10           0 S HEL Z/AU S HEL Z/AU
                E SHEARER G M/AU
L11         358 S E3 OR E6 OR E7
L12         118 S L11 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L13          20 S L12 AND (MAJOR HISTOCOMPATIBILITY OR CTL OR CYTOTOXIC)
                E NACSA J/AU
L14          22 S E3 OR E4

     FILE 'WPIDS' ENTERED AT 20:01:20 ON 01 APR 2004
                E FRANCHINI G/IN
L15          18 S E3
L16          10 S L15 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
                E SHEARER G M/IN
L17          10 S E3
L18          15 S E3 OR E2
                E NACSA J/IN
L19           3 S E3

     FILE 'USPATFULL' ENTERED AT 20:09:31 ON 01 APR 2004
L20       31746 S (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L21       10927 S L20 AND (CTL OR CYTOTOXIC)
L22        1761 S L21 AND (HIV/CLM OR HUMAN IMMUNODEFICIENCY VIRUS/CLM)
L23         233 S L22 AND (CTL/CLM OR CYTOTOXIC/CLM)
L24         186 S L23 AND (VACCIN? OR IMMUNOGEN?)
L25         182 S L24 AND (PROTECT? OR PREVENT?)
L26          96 S L25 AND (DNA/CLM OR NUCLEIC ACID/CLM)
L27          33 S L26 AND AY<2000
L28           1 S US6656471/PN
L29           1 S US6319666/PN

     FILE 'MEDLINE' ENTERED AT 20:22:25 ON 01 APR 2004
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L30        135974 S (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L31          5709 S L30 AND (CTL OR CYTOTOXIC T CELL? OR CYTOTOXIC T LYMPHOCYTE?
L32           176 S L31 AND (ESCAPE OR EVASION)
L33            78 S L32 AND (VACCIN? OR PREVENT? OR THERAP?)
L34            98 S L32 NOT L33

=> e koenig m/au
E1            4      KOENIG LINDA J/AU
E2            1      KOENIG LOISEAU M A/AU
E3          107 --> KOENIG M/AU
E4           32      KOENIG M A/AU
E5            2      KOENIG M B/AU
E6            3      KOENIG M E/AU
E7           64      KOENIG M G/AU
E8            2      KOENIG M H/AU
E9            2      KOENIG M J/AU
E10           1      KOENIG M K/AU
E11          14      KOENIG M L/AU
E12           2      KOENIG M L G/AU

=> s e3
L35          107 "KOENIG M"/AU

=> s l35 and (HIV or human immunodeficiency virus)
         135256 HIV
        8464764 HUMAN
         112466 IMMUNODEFICIENCY
         372233 VIRUS
          42485 HUMAN IMMUNODEFICIENCY VIRUS
                  (HUMAN(W)IMMUNODEFICIENCY(W)VIRUS)
L36             1 L35 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)

=> d l36,cbib

L36  ANSWER 1 OF 1     MEDLINE on STN
1998326767.    PubMed ID: 9663634.   Operation Red Box: a pilot project of
     needle and syringe drop boxes for injection drug users in East Baltimore.
     Riley E; Beilenson P; Vlahov D; Smith L; Koenig M; Jones T S; Doherty M.
     (Department of Epidemiology, The Johns Hopkins School of Hygiene and
     Public Health, Baltimore, Maryland, USA. ) Journal of acquired immune
     deficiency syndromes and human retrovirology : official publication of the
     International Retrovirology Association, (1998) 18 Suppl 1 S120-5.
     Journal code: 9501482. ISSN: 1077-9450. Pub. country: United States.
     Language: English.


=> s e4-e12
             32 "KOENIG M A"/AU
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              3 "KOENIG M E"/AU
             64 "KOENIG M G"/AU
              2 "KOENIG M H"/AU
              2 "KOENIG M J"/AU
              1 "KOENIG M K"/AU
             14 "KOENIG M L"/AU
              2 "KOENIG M L G"/AU
L37         122 ("KOENIG M A"/AU OR "KOENIG M B"/AU OR "KOENIG M E"/AU OR "KOENI
                G M G"/AU OR "KOENIG M H"/AU OR "KOENIG M J"/AU OR "KOENIG M
                K"/AU OR "KOENIG M L"/AU OR "KOENIG M L G"/AU)

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E2           14      KOENIG M L/AU
E3            2 --> KOENIG M L G/AU
E4            1      KOENIG M M/AU
E5           21      KOENIG M P/AU
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E6             1      KOENIG MARIE C/AU
E7             1      KOENIG MARRONY S/AU
E8             1      KOENIG MARRONY SEVERINE/AU
E9             1      KOENIG MARTIN E/AU
E10            1      KOENIG MATTHEW A/AU
E11            1      KOENIG MCINTYRE C/AU
E12            1      KOENIG MELISSA A/AU

=> s e1-e12
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              14 "KOENIG M L"/AU
               2 "KOENIG M L G"/AU
               1 "KOENIG M M"/AU
              21 "KOENIG M P"/AU
               1 "KOENIG MARIE C"/AU
               1 "KOENIG MARRONY S"/AU
               1 "KOENIG MARRONY SEVERINE"/AU
               1 "KOENIG MARTIN E"/AU
               1 "KOENIG MATTHEW A"/AU
               1 "KOENIG MCINTYRE C"/AU
               1 "KOENIG MELISSA A"/AU
L38           46 ("KOENIG M K"/AU OR "KOENIG M L"/AU OR "KOENIG M L G"/AU OR
                 "KOENIG M M"/AU OR "KOENIG M P"/AU OR "KOENIG MARIE C"/AU OR
                 "KOENIG MARRONY S"/AU OR "KOENIG MARRONY SEVERINE"/AU OR "KOENIG
                  MARTIN E"/AU OR "KOENIG MATTHEW A"/AU OR "KOENIG MCINTYRE C"/AU
                  OR "KOENIG MELISSA A"/AU)

=> e e12
E1             1      KOENIG MATTHEW A/AU
E2             1      KOENIG MCINTYRE C/AU
E3             1 -->  KOENIG MELISSA A/AU
E4             2      KOENIG MEREDIZ S A/AU
E5             5      KOENIG MICHAEL/AU
E6             3      KOENIG MICHAEL A/AU
E7             5      KOENIG MICHAEL L/AU
E8            10      KOENIG MICHEL/AU
E9             1      KOENIG MIRIAM/AU
E10            4      KOENIG N/AU
E11            2      KOENIG N H/AU
E12            1      KOENIG N M/AU

=> s e1-e12
               1 "KOENIG MATTHEW A"/AU
               1 "KOENIG MCINTYRE C"/AU
               1 "KOENIG MELISSA A"/AU
               2 "KOENIG MEREDIZ S A"/AU
               5 "KOENIG MICHAEL"/AU
               3 "KOENIG MICHAEL A"/AU
               5 "KOENIG MICHAEL L"/AU
              10 "KOENIG MICHEL"/AU
               1 "KOENIG MIRIAM"/AU
               4 "KOENIG N"/AU
               2 "KOENIG N H"/AU
               1 "KOENIG N M"/AU
L39           36 ("KOENIG MATTHEW A"/AU OR "KOENIG MCINTYRE C"/AU OR "KOENIG
                 MELISSA A"/AU OR "KOENIG MEREDIZ S A"/AU OR "KOENIG MICHAEL"/AU
                 OR "KOENIG MICHAEL A"/AU OR "KOENIG MICHAEL L"/AU OR "KOENIG
                 MICHEL"/AU OR "KOENIG MIRIAM"/AU OR "KOENIG N"/AU OR "KOENIG N
                 H"/AU OR "KOENIG N M"/AU)

=> d his

     (FILE 'HOME' ENTERED AT 19:42:02 ON 01 APR 2004)

     FILE 'USPATFULL' ENTERED AT 19:42:32 ON 01 APR 2004
                E FRANCHINI GENOVEFFA/IN
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L1              7 S E3
L2              0 S ZDENEK HEL/IN
                  E ZDENEK HEL/IN
L3              0 S HEL ZDENEK/IN S HEL ZDENEK/IN
L4              0 S GENE SHEARER/IN
L5              1 S SHEARER GENE/IN
                  E SHEARER GENE/IN
L6              7 S E4
                  E NACSA JANOS/IN

     FILE 'MEDLINE' ENTERED AT 19:47:38 ON 01 APR 2004
                  E FRANCHINI G/AU
L7            196 S E3 OR E4
L8             67 S L7 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L9             16 S L8 AND (MHC OR MAJOR HISTOCOMPATIBILITY OR CTL OR CYTOTOXIC T
L10             0 S HEL Z/AU S HEL Z/AU
                  E SHEARER G M/AU
L11           358 S E3 OR E6 OR E7
L12           118 S L11 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L13            20 S L12 AND (MAJOR HISTOCOMPATIBILITY OR CTL OR CYTOTOXIC)
                  E NACSA J/AU
L14            22 S E3 OR E4

     FILE 'WPIDS' ENTERED AT 20:01:20 ON 01 APR 2004
                  E FRANCHINI G/IN
L15            18 S E3
L16            10 S L15 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
                  E SHEARER G M/IN
L17            10 S E3
L18            15 S E3 OR E2
                  E NACSA J/IN
L19             3 S E3

     FILE 'USPATFULL' ENTERED AT 20:09:31 ON 01 APR 2004
L20         31746 S (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L21         10927 S L20 AND (CTL OR CYTOTOXIC)
L22          1761 S L21 AND (HIV/CLM OR HUMAN IMMUNODEFICIENCY VIRUS/CLM)
L23           233 S L22 AND (CTL/CLM OR CYTOTOXIC/CLM)
L24           186 S L23 AND (VACCIN? OR IMMUNOGEN?)
L25           182 S L24 AND (PROTECT? OR PREVENT?)
L26            96 S L25 AND (DNA/CLM OR NUCLEIC ACID/CLM)
L27            33 S L26 AND AY<2000
L28             1 S US6656471/PN
L29             1 S US6319666/PN

     FILE 'MEDLINE' ENTERED AT 20:22:25 ON 01 APR 2004
L30        139974 S (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L31          5709 S L30 AND (CTL OR CYTOTOXIC T CELL? OR CYTOTOXIC T LYMPHOCYTE?
L32           176 S L31 AND (ESCAPE OR EVASION)
L33            78 S L32 AND (VACCIN? OR PREVENT? OR THERAP?)
L34            98 S L32 NOT L33
                  E KOENIG M/AU
L35           107 S E3
L36             1 S L35 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L37           122 S E4-E12
                  E E12
L38            46 S E1-E12
                  E E12
L39            36 S E1-E12

=> s l37 or l38 or l39
L40           184 L37 OR L38 OR L39

=> s l40 and (HIV or human immunodeficiency virus)
        135256 HIV
       8464764 HUMAN
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        112400 IMMUNODEFICIENCY
        372233 VIRUS
         42485 HUMAN IMMUNODEFICIENCY VIRUS
                 (HUMAN(W)IMMUNODEFICIENCY(W)VIRUS)
L41           2 L40 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)

=> d l41,cbib,1-2

L41  ANSWER 1 OF 2     MEDLINE on STN
2003592565.    PubMed ID: 14672593.    Coercive sex in rural Uganda: prevalence
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     Nalugoda Fred; Kiwanuka Noah; Wabwire-Mangen Fred; Kigozi Godfrey;
     Sewankambo Nelson; Wagman Jennifer; Serwadda David; Wawer Maria; Gray Ron.
     (Department of Population and Family Health Sciences, Bloomberg School of
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     Baltimore, MD 21205, USA.. mkoenig@jhsph.edu) . Social science & medicine
     (1982), (2004 Feb) 58 (4) 787-98.  Journal code: 8303205. ISSN: 0277-9536.
     Pub. country: England: United Kingdom. Language: English.

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2003125409.    PubMed ID: 12640477.    Domestic violence in rural Uganda:
     evidence from a community-based study. Koenig Michael A; Lutalo Tom;
     Zhao Feng; Nalugoda Fred; Wabwire-Mangen Fred; Kiwanuka Noah; Wagman
     Jennifer; Serwadda David; Wawer Maria; Gray Ron. (Department of Population
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     Hopkins University, Baltimore, MD, USA.. mkoenig@jhsph.edu) . Bulletin of
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     7507052. ISSN: 0042-9686. Pub. country: Switzerland. Language: English.


=> d his

     (FILE 'HOME' ENTERED AT 19:42:02 ON 01 APR 2004)

     FILE 'USPATFULL' ENTERED AT 19:42:32 ON 01 APR 2004
                E FRANCHINI GENOVEFFA/IN
L1            7 S E3
L2            0 S ZDENEK HEL/IN
                E ZDENEK HEL/IN
L3            0 S HEL ZDENEK/IN S HEL ZDENEK/IN
L4            0 S GENE SHEARER/IN
L5            1 S SHEARER GENE/IN
                E SHEARER GENE/IN
L6            7 S E4
                E NACSA JANOS/IN

     FILE 'MEDLINE' ENTERED AT 19:47:38 ON 01 APR 2004
                E FRANCHINI G/AU
L7          196 S E3 OR E4
L8           67 S L7 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L9           16 S L8 AND (MHC OR MAJOR HISTOCOMPATIBILITY OR CTL OR CYTOTOXIC T
L10           0 S HEL Z/AU S HEL Z/AU
                E SHEARER G M/AU
L11         358 S E3 OR E6 OR E7
L12         118 S L11 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L13          20 S L12 AND (MAJOR HISTOCOMPATIBILITY OR CTL OR CYTOTOXIC)
                E NACSA J/AU
L14          22 S E3 OR E4

     FILE 'WPIDS' ENTERED AT 20:01:20 ON 01 APR 2004
                E FRANCHINI G/IN
L15          18 S E3
L16          10 S L15 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
                E SHEARER G M/IN
L17          10 S E3
L18          15 S E3 OR E2
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L19            3 S E3

     FILE 'USPATFULL' ENTERED AT 20:09:31 ON 01 APR 2004
L20        31746 S (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L21        10927 S L20 AND (CTL OR CYTOTOXIC)
L22         1761 S L21 AND (HIV/CLM OR HUMAN IMMUNODEFICIENCY VIRUS/CLM)
L23          233 S L22 AND (CTL/CLM OR CYTOTOXIC/CLM)
L24          186 S L23 AND (VACCIN? OR IMMUNOGEN?)
L25          182 S L24 AND (PROTECT? OR PREVENT?)
L26           96 S L25 AND (DNA/CLM OR NUCLEIC ACID/CLM)
L27           33 S L26 AND AY<2000
L28            1 S US6656471/PN
L29            1 S US6319666/PN

     FILE 'MEDLINE' ENTERED AT 20:22:25 ON 01 APR 2004
L30       139974 S (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L31         5709 S L30 AND (CTL OR CYTOTOXIC T CELL? OR CYTOTOXIC T LYMPHOCYTE?
L32          176 S L31 AND (ESCAPE OR EVASION)
L33           78 S L32 AND (VACCIN? OR PREVENT? OR THERAP?)
L34           98 S L32 NOT L33
                 E KOENIG M/AU
L35          107 S E3
L36            1 S L35 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L37          122 S E4-E12
                 E E12
L38           46 S E1-E12
                 E E12
L39           36 S E1-E12
L40          184 S L37 OR L38 OR L39
L41            2 S L40 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)

=> s l30 and py=1995
        416664 PY=1995
L42       9232 L30 AND PY=1995

=> s l42 and (CTL or cytotoxic T lymphocyte? or cytotoxic T cell? or CD8?)
         11061 CTL
         81352 CYTOTOXIC
       3621943 T
        357886 LYMPHOCYTE?
         11810 CYTOTOXIC T LYMPHOCYTE?
                 (CYTOTOXIC(W)T(W)LYMPHOCYTE?)
         81352 CYTOTOXIC
       3621943 T
       2479333 CELL?
          6698 CYTOTOXIC T CELL?
                 (CYTOTOXIC(W)T(W)CELL?)
         41255 CD8?
L43        407 L42 AND (CTL OR CYTOTOXIC T LYMPHOCYTE? OR CYTOTOXIC T CELL? OR
               CD8?)

=> s l43 and (therapy or immunotherapy or adoptive)
       2184984 THERAPY
         31705 IMMUNOTHERAPY
         10080 ADOPTIVE
L44         95 L43 AND (THERAPY OR IMMUNOTHERAPY OR ADOPTIVE)

=> s l44 not l32
L45         92 L44 NOT L32

=> d l45,cbib,1-92

L45  ANSWER 1 OF 92     MEDLINE on STN
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L45 ANSWER 3 OF 92 MEDLINE on STN
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L45 ANSWER 24 OF 92 MEDLINE on STN
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=> d l45,cbib,ab,48

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AB An **HIV**-1-seropositive volunteer was infused with an expanded autologous **cytotoxic T lymphocyte** (**CTL**) clone directed against the **HIV**-1 nef protein. This clone was adoptively transferred to determine whether supplementing **CTL** activity could reduce viral load or improve clinical course. Unexpectedly, infusion was followed by a decline in circulating CD4+ T cells and a rise in viral load. Some of the **HIV** isolates obtained from the plasma or CD4+ cells of the patient were lacking the nef epitope. These results suggest that active **CTL** selection of viral variants could contribute to the pathogenesis of AIDS and that clinical progression can occur despite high levels of circulating **HIV**-1-specific CTLs.

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     (FILE 'HOME' ENTERED AT 19:42:02 ON 01 APR 2004)

     FILE 'USPATFULL' ENTERED AT 19:42:32 ON 01 APR 2004
                E FRANCHINI GENOVEFFA/IN
L1            7 S E3
L2            0 S ZDENEK HEL/IN
                E ZDENEK HEL/IN
L3            0 S HEL ZDENEK/IN S HEL ZDENEK/IN
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L4              0 S GENE SHEARER/IN
L5              1 S SHEARER GENE/IN
                  E SHEARER GENE/IN
L6              7 S E4
                  E NACSA JANOS/IN

     FILE 'MEDLINE' ENTERED AT 19:47:38 ON 01 APR 2004
                  E FRANCHINI G/AU
L7            196 S E3 OR E4
L8             67 S L7 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L9             16 S L8 AND (MHC OR MAJOR HISTOCOMPATIBILITY OR CTL OR CYTOTOXIC T
L10             0 S HEL Z/AU S HEL Z/AU
                  E SHEARER G M/AU
L11           358 S E3 OR E6 OR E7
L12           118 S L11 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L13            20 S L12 AND (MAJOR HISTOCOMPATIBILITY OR CTL OR CYTOTOXIC)
                  E NACSA J/AU
L14            22 S E3 OR E4

     FILE 'WPIDS' ENTERED AT 20:01:20 ON 01 APR 2004
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L15            18 S E3
L16            10 S L15 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
                  E SHEARER G M/IN
L17            10 S E3
L18            15 S E3 OR E2
                  E NACSA J/IN
L19             3 S E3

     FILE 'USPATFULL' ENTERED AT 20:09:31 ON 01 APR 2004
L20         31746 S (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L21         10927 S L20 AND (CTL OR CYTOTOXIC)
L22          1761 S L21 AND (HIV/CLM OR HUMAN IMMUNODEFICIENCY VIRUS/CLM)
L23           233 S L22 AND (CTL/CLM OR CYTOTOXIC/CLM)
L24           186 S L23 AND (VACCIN? OR IMMUNOGEN?)
L25           182 S L24 AND (PROTECT? OR PREVENT?)
L26            96 S L25 AND (DNA/CLM OR NUCLEIC ACID/CLM)
L27            33 S L26 AND AY<2000
L28             1 S US6656471/PN
L29             1 S US6319666/PN

     FILE 'MEDLINE' ENTERED AT 20:22:25 ON 01 APR 2004
L30        139974 S (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L31          5709 S L30 AND (CTL OR CYTOTOXIC T CELL? OR CYTOTOXIC T LYMPHOCYTE?
L32           176 S L31 AND (ESCAPE OR EVASION)
L33            78 S L32 AND (VACCIN? OR PREVENT? OR THERAP?)
L34            98 S L32 NOT L33
                  E KOENIG M/AU
L35           107 S E3
L36             1 S L35 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L37           122 S E4-E12
                  E E12
L38            46 S E1-E12
                  E E12
L39            36 S E1-E12
L40           184 S L37 OR L38 OR L39
L41             2 S L40 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L42          9232 S L30 AND PY=1995
L43           407 S L42 AND (CTL OR CYTOTOXIC T LYMPHOCYTE? OR CYTOTOXIC T CELL?
L44            95 S L43 AND (THERAPY OR IMMUNOTHERAPY OR ADOPTIVE)
L45            92 S L44 NOT L32

=> s l31 and (fail?)
        489980 FAIL?
L46        310 L31 AND (FAIL?)
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=> s l46 not l32

L47 289 L46 NOT L32

=> d l47,cbib,1-289

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L47 ANSWER 279 OF 289 MEDLINE on STN
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L47 ANSWER 280 OF 289 MEDLINE on STN
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L47 ANSWER 281 OF 289 MEDLINE on STN
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L47 ANSWER 283 OF 289 MEDLINE on STN
89301782. PubMed ID: 2787146. Immune thrombocytopenia in hemophiliacs infected with **human immunodeficiency virus** and their response to splenectomy. Kim H C; Raska K Jr; Trooskin S; Saidi P. (Department of Medicine, University of Medicine and Dentistry, New Jersey-Robert Wood Johnson Medical School, New Brunswick 08903.) Archives of internal medicine, (1989 Jul) 149 (7) 1685-8. Journal code: 0372440. ISSN: 0003-9926. Pub. country: United States. Language: English.

L47 ANSWER 284 OF 289 MEDLINE on STN
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L47 ANSWER 285 OF 289 MEDLINE on STN
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country: United States. Language: English.

L47 ANSWER 286 OF 289 MEDLINE on STN
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L47 ANSWER 287 OF 289 MEDLINE on STN
89057146. PubMed ID: 2461519. **HIV**-1 gag-specific **cytotoxic T lymphocytes** defined with recombinant vaccinia virus and synthetic peptides. Nixon D F; Townsend A R; Elvin J G; Rizza C R; Gallwey J; McMichael A J. (Institute of Molecular Medicine, John Radcliffe Hospital, Oxford, UK.) Nature, (1988 Dec 1) 336 (6198) 484-7. Journal code: 0410462. ISSN: 0028-0836. Pub. country: ENGLAND: United Kingdom. Language: English.

L47 ANSWER 288 OF 289 MEDLINE on STN
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L47 ANSWER 289 OF 289 MEDLINE on STN
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L47 ANSWER 27 OF 289 MEDLINE on STN
2003043938. PubMed ID: 12553686. **HIV**-1 and AIDS: what are protective immune responses?. Beattie Tara; Rowland-Jones Sarah; Kaul Rupert. (Clinical Sciences Division, University of Toronto, Ontario, Canada.) Journal of HIV therapy, (2002 May) 7 (2) 35-9. Ref: 60. Journal code: 101088049. ISSN: 1462-0308. Pub. country: England: United Kingdom. Language: English.

AB **HIV**-1 is the leading cause of death in sub-Saharan Africa, responsible for one in five deaths in the region. Although potent antiretroviral therapy has had a huge impact on **HIV**-associated morbidity and mortality in economically advantaged countries, it is beyond the reach of most infected people in the world. The development of an effective **HIV** vaccine would be a huge step towards stopping the pandemic, but an important precondition for such a vaccine is that it must induce a host immune response that can protect the host from **HIV** acquisition or disease progression. This article reviews the evidence that protective host immune responses do exist, either in highly exposed, persistently seronegative (HEPS) subjects or in **HIV**-1-infected long-term non-progressors (LTNPs), as well as efforts to reproduce putative protective immunity in animal vaccine models. **HIV**-1-specific cellular responses are a key to viral control in infected subjects, but generally **fail** in the long term. This suggests that the goal of a preventive **HIV**-1 vaccine should be sterile immunity, rather than improved virus control after infection. Achieving this goal will at least require the induction of **HIV**-1-specific cellular immune responses at the site of initial viral contact (generally the genital tract), perhaps in

combination with **HIV** 1 specific neutralising antibody.

L47 ANSWER 34 OF 289 MEDLINE on STN
2002654780. PubMed ID: 12414957. Direct binding of **human immunodeficiency virus** type 1 Nef to the major histocompatibility complex class I (MHC-I) cytoplasmic tail disrupts MHC-I trafficking. Williams Maya; Roeth Jeremiah F; Kasper Matthew R; Fleis Rebekah I; Przybycin Chris G; Collins Kathleen L. (Graduate Program in Cellular and Molecular Biology, University of Michigan. University of Michigan School of Medicine, Ann Arbor, Michigan 48109, USA.) Journal of virology, (2002 Dec) 76 (23) 12173-84. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Nef, an essential pathogenic determinant for **human immunodeficiency virus** type 1, has multiple functions that include disruption of major histocompatibility complex class I molecules (MHC-I) and CD4 and CD28 cell surface expression. The effects of Nef on MHC-I have been shown to protect infected cells from **cytotoxic T-lymphocyte** recognition by downmodulation of a subset of MHC-I (HLA-A and -B). The remaining HLA-C and -E molecules prevent recognition by natural killer (NK) cells, which would otherwise lyse cells expressing small amounts of MHC-I. Specific amino acid residues in the MHC-I cytoplasmic tail confer sensitivity to Nef, but their function is unknown. Here we show that purified Nef binds directly to the HLA-A2 cytoplasmic tail in vitro and that Nef forms complexes with MHC-I that can be isolated from human cells. The interaction between Nef and MHC-I appears to be weak, indicating that it may be transient or stabilized by other factors. Supporting the fact that these molecules interact in vivo, we found that Nef colocalizes with HLA-A2 molecules in a perinuclear distribution inside cells. In addition, we demonstrated that Nef **fails** to bind the HLA-E tail and also **fails** to bind HLA-A2 tails with deletions of amino acids necessary for MHC-I downmodulation. These data provide an explanation for differential downmodulation of MHC-I allotypes by Nef. In addition, they provide the first direct evidence indicating that Nef functions as an adaptor molecule able to link MHC-I to cellular trafficking proteins.

L47 ANSWER 36 OF 289 MEDLINE on STN
2002633315. PubMed ID: 12370434. Stimulation of **HIV**-specific cellular immunity by structured treatment interruption **fails** to enhance viral control in chronic **HIV** infection. Oxenius Annette; Price David A; Gunthard Huldrych F; Dawson Sara J; Fagard Catherine; Perrin Luc; Fischer Marek; Weber Rainer; Plana Montserrat; Garcia Felipe; Hirschel Bernard; McLean Angela; Phillips Rodney E. (Nuffield Department of Medicine, John Radcliffe Hospital and Peter Medawar Building for Pathogen Research, Oxford OX1 3SY, UK.. oxenius@micro.biol.ethz.ch) . Proceedings of the National Academy of Sciences of the United States of America, (2002 Oct 15) 99 (21) 13747-52. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB Potent antiretroviral therapy (ART) suppresses **HIV**-1 viral replication and results in decreased morbidity and mortality. However, prolonged treatment is associated with drug-induced toxicity, emergence of drug-resistant viral strains, and financial constraints. Structured therapeutic interruptions (STIs) have been proposed as a strategy that could boost **HIV**-specific immunity, through controlled exposure to autologous virus over limited time periods, and subsequently control viral replication in the absence of ART. Here, we analyzed the impact of repeated STIs on virological and immunological parameters in a large prospective STI study. We show that: (i) the plateau virus load (VL) reached after STIs correlated with pretreatment VL, the amount of viral recrudescence during the treatment interruptions, and the off-treatment viral rebound rate; (ii) the magnitude and the breadth of the **HIV**-specific **CD8**(+) T lymphocyte response, despite marked interpatient variability, increased overall with STI. However, the quantity and quality of the post-STI response was comparable to the response observed before any therapy; (iii) individuals with strong and broad **HIV**-specific **CD8**(+) T lymphocyte responses at baseline retained these characteristics during and after STI; (iv) the increase in **HIV**-specific **CD8**(+) T

lymphocyte frequencies induced by STI was not correlated with decreased viral set point after STI; and (v) **HIV**-specific CD4(+) T lymphocyte responses increased with STI, but were subsequently maintained only in patients with low pretreatment and plateau VLs. Overall, these data indicate that STI-induced quantitative boosting of **HIV**-specific cellular immunity was not associated with substantial change in viral replication and that STI was largely restoring pretherapy **CD8**(+) T cell responses in patients with established infection.

L47 ANSWER 56 OF 289 MEDLINE on STN
2002136589. PubMed ID: 11871389. Why antiviral **CD8** T lymphocytes **fail** to prevent progressive immunodeficiency in **HIV**-1 infection. Agostini Carlo; Semenzato Gianpietro. Blood, (2002 Mar 1) 99 (5) 1876-7. Journal code: 7603509. ISSN: 0006-4971. Pub. country: United States. Language: English.

L47 ANSWER 96 OF 289 MEDLINE on STN
2001182600. PubMed ID: 11181148. Alterations in T cell phenotype and **human immunodeficiency virus** type 1-specific cytotoxicity after potent antiretroviral therapy. Seth A; Markee J; Hoering A; Sevin A; Sabath D E; Schmitz J E; Kuroda M J; Lifton M A; Hirsch M S; Collier A C; Letvin N L; McElrath M J. (Division of Viral Pathogenesis, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA.) Journal of infectious diseases, (2001 Mar 1) 183 (5) 722-9. Journal code: 0413675. ISSN: 0022-1899. Pub. country: United States. Language: English.

AB **Cytotoxic T lymphocytes** (CTLs) are an important defense against **human immunodeficiency virus** (**HIV**) type 1 but ultimately **fail** to control infection. To determine whether more efficient sustained immunity is induced by suppressing replication, the evolution of T cell phenotypes and **HIV**-specific **CD8**+ lymphocytes was prospectively investigated in 41 patients initiating combination therapy. Suppression of viremia to <200 copies/mL was associated with increases in naive cells (CD45RA+62L+) and declines in activated T cells (CD95+ cell counts and CD38+ HLA-DR+). **HIV**-specific tetramer-staining **CD8**+ T cells were detected in 6 of 10 HLA-A*0201-positive persons, which declined in 5 with treatment. **CTL** precursor frequencies were markedly consistent before and after treatment. Eight (72%) of 11 recognized > or =1 immunodominant epitope, representing either a new or an increased **CTL** response after treatment. Thus, activated **CD8**+ T cells, including those recognizing immunodominant epitopes, decline with combination therapy. However, the overall level of antigen-specific cells that are capable of differentiating into effectors remains stable, and the recognition of new epitopes may occur.

L47 ANSWER 99 OF 289 MEDLINE on STN
2001130534. PubMed ID: 11142629. **HIV** immunotherapeutic vaccines. Peters B S. (Department of GU Medicine, GKT School of Medicine, St Thomas' Hospital, London, UK.. barry@bpeters.demon.co.uk) . Antiviral chemistry & chemotherapy, (2000 Sep) 11 (5) 311-20. Ref: 73. Journal code: 9009212. ISSN: 0956-3202. Pub. country: England: United Kingdom. Language: English.

AB New combinations of antiretrovirals have improved the quality of life and length of survival of patients with **HIV** infection and AIDS, but they have significant disadvantages. These include considerable toxicity, the development of drug resistance and expense. Successful immunotherapeutic vaccination against **HIV** would overcome these problems. None of the approaches that have been tried so far have shown a sufficient effect on **HIV** replication or on immunorestoration to merit their introduction to clinical practice. The most developed agent thus far is Remune, a gp120 depleted whole killed **HIV**-1 vaccine that has shown marked **cytotoxic T lymphocyte** responses when administered to man. CD4 count and **HIV**-1 viral load responses have occurred, but have so far been disappointing in their magnitude. Remune is entering Phase III trials in North America, Europe and the Far East, to determine clinical efficacy. Immunization using recombinant **HIV** envelope proteins, such as rgp160, for example with VaxSyn, have **failed** to produce a therapeutic response. Similarly, agents using **HIV** core antigens, such as p24VLP, have also

failed to work. Hence, newer strategies have been tried. Recombinant canarypox vaccines like ALVAC 1452 and highly attenuated vaccinia virus vaccines, such as NYVAC, have been used in combination with **HIV** genes and peptides. Preliminary results suggest that they might reduce the **HIV** replication rate, but this needs confirming in larger clinical trials. DNA vaccination has produced encouraging results in monkeys, but the success has not yet been repeated in humans. Other strategies at an early stage include the exploitation of the protective alloimmune response in man. Outside the immunotherapeutic area, other promising new strategies that are being developed in parallel, include the fusion inhibitors, such as T-20. The potential benefits from a successful immunotherapeutic vaccine dictate that this area should, and will receive priority.

L47 ANSWER 118 OF 289 MEDLINE on STN
2000252025. PubMed ID: 10794051. A new theory of **cytotoxic T-lymphocyte** memory: implications for **HIV** treatment. Wodarz D; Page K M; Arnaout R A; Thomsen A R; Lifson J D; Nowak M A. (Institute for Advanced Study, Princeton, NJ 08540, USA.. wodarz@ias.edu) . Philosophical transactions of the Royal Society of London. Series B, Biological sciences, (2000 Mar 29) 355 (1395) 329-43. Ref: 67. Journal code: 7503623. ISSN: 0962-8436. Pub. country: ENGLAND: United Kingdom. Language: English.

AB We use simple mathematical models to examine the dynamics of primary and secondary **cytotoxic T-lymphocyte** (**CTL**) responses to viral infections. In particular, we are interested in conditions required to resolve the infection and to protect the host upon secondary challenge. While protection against reinfection is only effective in a restricted set of circumstances, we find that resolution of the primary infection requires persistence of **CTL** precursors (GTLp), as well as a fast rate of activation of the CTLp. Since these are commonly the defining characteristics of **CTL** memory, we propose that **CTL** memory may have evolved in order to clear the virus during primary challenge. We show experimental data from lymphocytic choriomeningitis virus infection in mice, supporting our theory on **CTL** memory. We adapt our models to **HIV** and find that immune impairment during the primary phase of the infection may result in the **failure** to establish **CTL** memory which in turn leads to viral persistence. Based on our models we suggest conceptual treatment regimes which ensure establishment of **CTL** memory. This would allow the immune response to control **HIV** in the long term in the absence of continued therapy.

L47 ANSWER 127 OF 289 MEDLINE on STN
2000135872. PubMed ID: 10671225. Effect of pre-existing **cytotoxic T lymphocytes** on therapeutic vaccines. Sherritt M A; Gardner J; Elliott S L; Schmidt C; Purdie D; Deliyannis G; Heath W R; Suhrbier A. (Australian National Centre for International & Tropical Health & Nutrition, Queensland Institute of Medical Research and the University of Queensland, Royal Brisbane Hospital, Brisbane, Australia.) European journal of immunology, (2000 Feb) 30 (2) 671-7. Journal code: 1273201. ISSN: 0014-2980. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB Therapeutic vaccines which aim to induce **CD8**(+) **cytotoxic T lymphocyte** (**CTL**) responses will often be required to perform in the presence of pre-existing **CTL** which recognize epitopes within the vaccine. Here we explore the ability of a viral vaccine vector presenting several co-dominant **CTL** epitopes to prime **CTL** responses in animals that have a pre-existing **CTL** response to one of the epitopes in the vaccine. The vaccine was usually capable of inducing multiple new responses, suggesting that immunodomination effects of pre-existing **CTL** may generally be minimal following vaccination. However, when large numbers of pre-existing **CTL** were present, a novel type of immune modulation was observed whereby (1) the vaccine **failed** to prime efficiently new **CTL** responses that were restricted by the same MHC gene as the pre-existing responses, and (2) vaccine-induced **CTL** responses restricted by other MHC genes were enhanced. These results may have

implications for therapeutic multi epitope vaccines for diseases like **HIV** and melanoma, which aim to broaden **CTL** responses.

L47 ANSWER 134 OF 289 MEDLINE on STN
2000015399. PubMed ID: 10547676. DNA vaccines: a review. Lewis P J; Babiuk L A. (Veterinary Infectious Disease Organization, University of Saskatchewan, Saskatoon, Canada.) Advances in virus research, (1999) 54 129-88. Ref: 180. Journal code: 0370441. ISSN: 0065-3527. Pub. country: United States. Language: English.

AB Therapeutic and prophylactic DNA vaccine clinical trials for a variety of pathogens and cancers are underway (Chattergoon et al., 1997; Taubes, 1997). The speed with which initiation of these trials occurred is no less than astounding; clinical trials for a **human immunodeficiency virus** (**HIV**) gp160 DNA-based vaccine were underway within 36 months of the first description of "genetic immunization" (Tang et al., 1992) and within 24 months of publication of the first article describing intramuscular delivery of a DNA vaccine (Ulmer et al., 1993). Despite the relative fervor with which clinical trials have progressed, it can be safely stated that DNA-based vaccines will not be an immunological "silver bullet." In this regard, it was satisfying to see a publication entitled "DNA Vaccines--A Modern Gimmick or a Boon to Vaccinology?" (Manickan et al., 1997b). There is no doubt that this technology is well beyond the phenomenology phase of study. Research niches and models have been established and will allow the truly difficult questions of mechanism and application to target species to be studied. These two aspects of future studies are intricately interwoven and will ultimately determine the necessity for mechanistic understanding and the evolution of target species studies. The basic science of DNA vaccines has yet to be clearly defined and will ultimately determine the success or **failure** of this technology to find a place in the immunological arsenal against disease. In a commentary on a published study describing DNA vaccine-mediated protection against heterologous challenge with **HIV**-1 in chimpanzees, Ronald Kennedy (1997) states, "As someone who has been in the trenches of AIDS vaccine research for over a decade and who, together with collaborators, has attempted a number of different vaccine approaches that have not panned out, I have a relatively pessimistic view of new AIDS vaccine approaches." Kennedy then goes on to summarize a DNA-based multigene vaccine approach and the subsequent development of neutralizing titers and potent **CTL** activity in immunized chimpanzees (Boyer et al., 1997). Dr. Kennedy closes his commentary by stating. "The most exciting aspect of this report is the experimental challenge studies.... Viraemia was extremely transient and present at low levels during a single time point. These animals remained seronegative ... for one year after challenge" and "Overall, these observations engender some excitement". (Kennedy, 1997). Although this may seem a less than rousing cheer for DNA vaccine technology, it is a refreshingly hopeful outlook for a pathogen to which experience has taught humility. It has also been suggested that DNA vaccine technology may find its true worth as a novel alternative option for the development of vaccines against diseases that conventional vaccines have been unsuccessful in controlling (Manickan et al., 1997b). This is a difficult task for any vaccine, let alone a novel technology. DNA-based vaccine technology represents a powerful and novel entry into the field of immunological control of disease. The spinoff research has also been dramatic, and includes the rediscovery of potent bacterially derived immunomodulatory DNA sequences (Gilkeson et al., 1989), as well as availability of a methodology that allows extremely rapid assessment and dissection of both antigens and immunity. The benefits of potent Th1-type immune responses to DNA vaccines must not be overlooked, particularly in the light of suggestions that Western culture immunization practices may be responsible for the rapid increases in adult allergic and possibly autoimmune disorders (Rook and Stanford, 1998). The full utility of this technology has not yet been realized, and yet its broad potential is clearly evident. Future investigations of this technology must not be hindered by impatience, misunderstanding, and lack of funding or **failure** of an informed collective and collaborative effort.

L47 ANSWER 157 OF 289 MEDLINE on STN
1999454505. PubMed ID: 10527381. Analysis of the mutant HLA-A*0201 heavy chain H74L: impaired TAP-dependent peptide loading. Caley R R; Peace-Brewer A L; Matsui M; Frelinger J A. (Department of Microbiology and Immunology, University of North Carolina at Chapel Hill, 27599-7290, USA.) Human immunology, (1999 Sep) 60 (9) 743-54. Journal code: 8010936. ISSN: 0198-8859. Pub. country: United States. Language: English.

AB A mutation of the HLA-A*0201 heavy chain at position 74 from histidine to leucine (H74L) resulted in a molecule with an interesting phenotype. H74L-expressing targets were recognized by peptide-specific HLA-A*0201-restricted **cytotoxic T lymphocytes** at lower peptide concentrations than wild type HLA-A*0201. H74L's improved ability to sensitize cells for tysis was due to its enhanced capability to bind exogenous peptide. Furthermore, this phenotype of improved exogenous binding and functional recognition was not peptide-specific. In contrast, the H74L molecule **failed** to present the **HIV**- HLA-A2-restricted pol peptide when expressed and processed endogenously. The inability to bind endogenous pol could be rescued by preceding the pol peptide with a signal sequence. The defect affecting endogenous presentation, therefore, appeared to be limited to the TAP-dependent pathway. Surprisingly, the H74L heavy chain was able to enter the defined MHC class I pathway and associate with beta2M, calreticulin, tapasin, and TAP. Despite the presence of the H74L heavy chain at the TAP complex, H74L was functionally inefficient at loading TAP-dependent peptides. H74L may help elucidate further steps in the process of loading TAP-dependent peptides into the class I cleft.

L47 ANSWER 153 OF 289 MEDLINE on STN
1999131403. PubMed ID: 9934704. Role of class I major histocompatibility complex-restricted and -unrestricted suppression of **human immunodeficiency virus** type 1 replication by **CD8**+ T lymphocytes. Ohashi T; Kubo M; Kato H; Iwamoto A; Takahashi H; Fujii M; Kannagi M. (Department of Immunotherapeutics, Tokyo Medical and Dental University, Japan.) Journal of general virology, (1999 Jan) 80 (Pt 1) 209-16. Journal code: 0077340. ISSN: 0022-1317. Pub. country: ENGLAND: United Kingdom. Language: English.

AB **CD8**+ T lymphocytes of asymptomatic **human immunodeficiency virus** type 1 (**HIV**-1) carriers (ACs) are capable of suppressing **HIV**-1 replication in CD4+ peripheral blood mononuclear cells (PBMC) by a variety of known and unknown mechanisms. In the present study, cell contact-dependent, major histocompatibility complex type I (MHC I)-unrestricted, **CD8**+ cell-mediated suppression of **HIV**-1 LAI replication was detected. **CD8**+ PBMC of ACs suppressed **HIV**-1 replication more efficiently in MHC I-matched CD4+ PBMC than in mismatched cells. However, even when MHC I was totally mismatched, **CD8**+ cells still suppressed replication to a considerable extent in CD4+ PBMC. This MHC I-unrestricted, **CD8**+ cell-mediated **HIV**-1 suppression required cell contact and was not effective against cells of the established T cell line ILT-KK. In contrast, MHC I-restricted **HIV**-1 suppression by **CD8**+ T cells was detected when ILT-KK cells were used as a target. By using these systems, we examined MHC I-restricted and -unrestricted suppressive activities of **CD8**+ cells in various donors in more detail. Although both types of **CD8**+ cell-mediated **HIV**-1 suppression diminished at the advanced stage of the infection, MHC I-unrestricted suppression diminished earlier than MHC I-restricted suppression, in parallel with the decline in CD4+ T cells. These results suggest that suppression by the MHC I-restricted mechanism alone may **fail** to protect against CD4+ T-cell loss at the late stage of infection.

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L47 ANSWER 166 OF 289 MEDLINE on STN
1998208574. PubMed ID: 9539771. Copresentation of natural **HIV**-1 agonist and antagonist ligands **fails** to induce the T cell receptor signaling cascade. Purbhoo M A; Sewell A K; Klenerman P; Goulder P J; Hilyard K L;

Bell J I; Jakobsen B K; Phillips R E. (University of Oxford, Nuffield Department of Medicine and Institute of Molecular Medicine, John Radcliffe Hospital, Headington, Oxford OX3 9DU, United Kingdom.) Proceedings of the National Academy of Sciences of the United States of America, (1998 Apr 14) 95 (8) 4527-32. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB It is not known how **human immunodeficiency virus** type 1 (**HIV**-1)-derived antagonist peptides interfere with intracellular activation of **cytotoxic T lymphocytes** (**CTL**). We identified Gag epitope variants in **HIV**-1-infected patients that act as antagonists of **CTL** responses to unmutated epitopes. We then investigated the effect that presentation of each variant has on the early events of T cell receptor (TCR) signal transduction. We found that altered peptide ligands (APL) **failed** to induce phosphorylation of pp36, a crucial adaptor protein involved in TCR signal transduction. We further investigated the effect that simultaneous presentation of APL and native antigen at low, physiological, peptide concentrations (1 nM) has on TCR signal transduction, and we found that the presence of APL can completely inhibit induction of the protein tyrosine phosphorylation events of the TCR signal transduction cascade.

L47 ANSWER 171 OF 289 MEDLINE on STN

1998102440. PubMed ID: 9427713. Circulating **CD8** T lymphocytes in **human immunodeficiency virus**-infected individuals have impaired function and downmodulate CD3 zeta, the signaling chain of the T-cell receptor complex. Trimble L A; Lieberman J. (Center for Blood Research, Harvard Medical School, Boston, MA, USA.) Blood, (1998 Jan 15) 91 (2) 585-94. Journal code: 7603509. ISSN: 0006-4971. Pub. country: United States. Language: English.

AB Although **human immunodeficiency virus** (**HIV**)-infected subjects without acquired immunodeficiency syndrome have a high frequency of **HIV**-specific **CD8** T lymphocytes, freshly isolated lymphocytes frequently lack detectable **HIV**-specific cytotoxicity. However, this effector function becomes readily apparent after overnight culture. To investigate reasons for T-cell dysfunction, we analyzed T-cell expression of the cytolytic protease granzyme A and CD3 zeta, the signaling component of the T-cell receptor complex. An increased proportion of CD4 and **CD8** T cells from **HIV**-infected donors contain granzyme A, consistent with the known increased frequency of activated T cells. In 28 **HIV**-infected donors with mild to advanced immunodeficiency, a substantial fraction of circulating T cells downmodulated CD3 zeta (fraction of T cells expressing CD3 zeta, 0.74 +/- 0.16 v 1.01 +/- 0.07 in healthy donors; P < .0000005). CD3 zeta expression is downregulated more severely in **CD8** than CD4 T cells, decreases early in infection, and correlates with declining CD4 counts and disease stage. CD3 zeta expression increases over 6 to 16 hours of culture in an interleukin-2-dependent manner, coincident with restoration of viral-specific cytotoxicity. Impaired T-cell receptor signaling may help explain why **HIV**-specific **cytotoxic T lymphocytes fail** to control **HIV** replication.

L47 ANSWER 174 OF 289 MEDLINE on STN

1998070938. PubMed ID: 9405267. T-cell homeostasis in **HIV**-1 infection. Margolick J B; Donnenberg A D. (Johns Hopkins University School of Hygiene and Public Health, Baltimore, MD, USA.) Seminars in immunology, (1997 Dec) 9 (6) 381-8. Ref: 29. Journal code: 9009458. ISSN: 1044-5323. Pub. country: United States. Language: English.

AB **Failure** of T-cell homeostasis is an important feature of **HIV**-1 infection. Substantial evidence indicates that T-cell homeostasis is independent of CD4+ and **CD8**+ subsets, and this may contribute to the decline of CD4+ T cells to low levels in this disease. Moreover, **failure** of T-cell homeostasis appears to precede the development of clinically-defined AIDS by approximately 1.5 to 2 years and is thus an important milestone in **HIV**-1 disease progression. We argue that T-cell turnover and depletion of memory cells in **HIV**-1 infection can be viewed as the reverse of the process by which immune reconstitution occurs after stem cell transplantation, and that changes in the functional level of

T cell memory may be critical to both processes. An understanding of the relationship between T-cell memory and regeneration of lost T cells may help preserve and/or reconstitute immune system homeostasis in **HIV**-1-infected individuals.

L47 ANSWER 180 OF 289 MEDLINE on STN
97420772. PubMed ID: 9275214. Evidence for rapid disappearance of initially expanded **HIV**-specific **CD8**+ T cell clones during primary **HIV** infection. Pantaleo G; Soudeyns H; Demarest J F; Vaccarezza M; Graziosi C; Paolucci S; Daucher M; Cohen O J; Denis F; Biddison W E; Sekaly R P; Fauci A S. (Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892, USA.. Giuseppe.Pantaleo@chuv.hospvd.ch) . Proceedings of the National Academy of Sciences of the United States of America, (1997 Sep 2) 94 (18) 9848-53. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB Down-regulation of the initial burst of viremia during primary **HIV** infection is thought to be mediated predominantly by **HIV**-specific **cytotoxic T lymphocytes**, and the appearance of this response is associated with major perturbations of the T cell receptor repertoire. Changes in the T cell receptor repertoire of virus-specific **cytotoxic T lymphocytes** were analyzed in patients with primary infection to understand the **failure** of the cellular immune response to control viral spread and replication. This analysis demonstrated that a significant number of **HIV**-specific T cell clones involved in the primary immune response rapidly disappeared. The disappearance was not the result of mutations in the virus epitopes recognized by these clones. Evidence is provided that phenomena such as high-dose tolerance or clonal exhaustion might be involved in the disappearance of these monoclonally expanded **HIV**-specific **cytotoxic T cell** clones. These findings should provide insights into how **HIV**, and possibly other viruses, elude the host immune response during primary infection.

L47 ANSWER 190 OF 289 MEDLINE on STN
97258622. PubMed ID: 9104816. The **human immunodeficiency virus** type 1 (**HIV**-1) Vpu protein interferes with an early step in the biosynthesis of major histocompatibility complex (MHC) class I molecules. Kerkau T; Bacik I; Bennink J R; Yewdell J W; Hunig T; Schimpl A; Schubert U. (Institute of Virology and Immunobiology, University of Wurzburg, Germany.) Journal of experimental medicine, (1997 Apr 7) 185 (7) 1295-305. Journal code: 2985109R. ISSN: 0022-1007. Pub. country: United States. Language: English.

AB The **human immunodeficiency virus** type 1 (**HIV**-1) vpu gene encodes a small integral membrane phosphoprotein with two established functions: degradation of the viral coreceptor CD4 in the endoplasmic reticulum (ER) and augmentation of virus particle release from the plasma membrane of **HIV**-1-infected cells. We show here that Vpu is also largely responsible for the previously observed decrease in the expression of major histocompatibility complex (MHC) class I molecules on the surface of **HIV**-1-infected cells. Cells infected with **HIV**-1 isolates that **fail** to express Vpu, or that express genetically modified forms of Vpu that no longer induce CD4 degradation, exhibit little downregulation of MHC class I molecules. The effect of Vpu on class I biogenesis was analyzed in more detail using a Vpu-expressing recombinant vaccinia virus (VV). VV-expressed Vpu induces the rapid loss of newly synthesized endogenous or VV-expressed class I heavy chains in the ER, detectable either biochemically or by reduced cell surface expression. This effect is of similar rapidity and magnitude as the VV-expressed Vpu-induced degradation of CD4. Vpu had no discernible effects on cell surface expression of VV-expressed mouse CD54, demonstrating the selectivity of its effects on CD4 and class I heavy chains. VV-expressed Vpu does not detectably affect class I molecules that have been exported from the ER. The detrimental effects of Vpu on class I molecules could be distinguished from those caused by VV-expressed herpes virus protein ICP47, which acts by decreasing the supply of cytosolic peptides to class I molecules,

indicating that vpu functions in a distinct manner from ICP47. Based on these findings, we propose that Vpu-induced downregulation of class I molecules may be an important factor in the evolutionary selection of the **HIV**-1-specific vpu gene by contributing to the inability of **CD8**+ T cells to eradicate **HIV**-1 from infected individuals.

L47 ANSWER 218 OF 289 MEDLINE on STN
95378698. PubMed ID: 7544382. Immunogenic **HIV** variant peptides that bind to HLA-B8 can **fail** to stimulate **cytotoxic T lymphocyte** responses. McAdam S; Klenerman P; Tussey L; Rowland-Jones S; Lalloo D; Phillips R; Edwards A; Giangrande P; Brown A L; Gotch F; +. (Institute of Molecular Medicine, John Radcliffe Hospital, Headington, Oxford, UK.) Journal of immunology (Baltimore, Md. : 1950), (1995 Sep 1) 155 (5) 2729-36. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB **Cytotoxic T lymphocyte** responses in **HIV** infection can be impaired through variation in the epitope regions of viral proteins such as a gag. We report here an analysis of variant epitope peptides in three gag epitopes presented by HLA B8. Fifteen variant peptides were examined for their binding to HLA-B8; all but one bound at concentrations comparable to known epitopes. All except two of those that bound could be recognized by **CTL** from an HLA-B8 positive **HIV**-1-infected patient and were therefore immunogenic. However, in a hemophiliac patient studied in detail, there was a **failure** to respond to two immunogenic peptide epitopes representing virus present as provirus in the patient's peripheral blood. In one case, the patient's **CTL** had previously responded to the peptide; in the other case, there was a good response to a peptide of closely related sequence. Thus there was a selective **failure** of the **CTL** response to some proviral epitopes. This impaired reaction to new variants could contribute to the loss of immune control of the infection.

=> d 147,cbib,ab,264,260,255,243,242,236,226,154,203,90

L47 ANSWER 264 OF 289 MEDLINE on STN
91215645. PubMed ID: 1708701. **HIV**-related alterations in **CD8** cell subsets defined by in vitro survival characteristics. Prince H E; Jensen E R. (American Red Cross Blood Services, Los Angeles, California 90006.) Cellular immunology, (1991 May) 134 (2) 276-86. Journal code: 1246405. ISSN: 0008-8749. Pub. country: United States. Language: English.

AB Previously we showed that over 50% of **CD8** cells from **HIV**-infected persons do not survive in 3-day cultures of mononuclear cells; this loss occurred preferentially in subsets with phenotypes indicative of in vivo activation. In the studies reported here, we asked if cytokines enhanced **CD8** cell survival. Of IL1, IL2, IL4, IL6, tumor necrosis factor, and interferon-gamma only IL2 specifically enhanced **CD8** survival in the **HIV** group, compared to the control group. Further studies thus focused on characterizing **CD8** cell survival in the presence of IL2. In both study groups, three subsets of **CD8** cells were identified based on in vitro survival: (a) those surviving in culture medium alone (survivors), (b) those surviving only when IL2 was included in the culture medium (IL2-dependent survivors), and (c) those **failing** to survive even in the presence of IL2 (nonsurvivors). By dual-color cytofluorometry, the **CD8** survivor subset was similar in the two study groups, and expressed nonactivated phenotypes (Leu8+, CD45RA+, HLA-DR-). The IL2-dependent survivor subset was also similar in the two study groups and expressed the phenotypes Leu8-, CD45RA+, CD57+, HLA-DR+, and CD38+, suggesting prior activation. The **CD8** nonsurvivor subset, in contrast, was markedly different in the study groups: compared to the control group, the **HIV** group contained significantly higher proportions of **CD8** cells expressing the phenotypes Leu8-, CD57+, and HLA-DR+, also suggesting activation. These findings indicate that, in **HIV** infection, the activated **CD8** cell subsets that do not survive in medium alone consist of a "normal" component that requires IL2 for survival and an "abnormal" component that does not survive even in IL2.

L47 ANSWER 260 OF 289 MEDLINE on STN
92075351. PubMed ID: 1742084. Selective stimulation of CD4+ versus **CD8**+ T-cell subsets in symptomatic and asymptomatic **HIV**-1-infected individuals. Bettens F; Pichler C E; Herrmann B; de Weck A L; Pichler W J. (Institute for Clinical Immunology, Inselspital, Bern, Switzerland.) AIDS research and human retroviruses, (1991 Sep) 7 (9) 773-80. Journal code: 8709376. ISSN: 0889-2229. Pub. country: United States. Language: English.

AB To analyze the proliferative capacity of CD4+ or **CD8**+ T-cell subsets of individuals infected with **human immunodeficiency virus** type 1 (**HIV**-1) and to optimize the in vitro conditions for virus replication, CD4+ or **CD8**+ cells of **HIV**-1-infected patients were selectively activated inside the whole peripheral blood mononuclear cell (PMNC) population by dual antibody stimulation. To do so PMNC of **HIV**-1-infected individuals were stimulated with the per se nonmitogenic anti-CD3 antibody fragment BMA030 F(ab)2 crosslinked through goat antimouse antibodies with an anti-CD4 or an anti-**CD8** antibody, which lead to selective proliferation of either the CD4+ or the **CD8**+ T-cell subset. In the presence of monocyte supernatant and recombinant interleukin-2 (rIL2) CD4+ cells of **HIV**-1 patients responded normally upon such stimulation as their proliferation correlated (r = 0.9) to the percentage CD4+ cells present in the PMNC population. Selective stimulation and proliferation of **CD8**+ cells could, however, only partially be elicited by dual antibody stimulation, even in the presence of rIL-2 and monocyte supernatant. Their proliferative response did not correspond (r = 0.1) to the percentage **CD8**+ cells present in the PMNC culture. A positive correlation (r = 0.7) was detected only between percentage **CD8**+ HLA-DR- cells and proliferation. This confirmed previous studies showing that the defective in vitro proliferative response of peripheral blood lymphocytes of **HIV**-infected individuals to mitogens, which is usually interpreted being due to a CD4 cell defect, is actually due to a **failure** of **CD8**+DR+ cells to proliferate.(ABSTRACT TRUNCATED AT 250 WORDS)

L47 ANSWER 255 OF 289 MEDLINE on STN
92219406. PubMed ID: 1373204. Mutation of **human immunodeficiency virus** type 1 at amino acid 585 on gp41 results in loss of killing by **CD8**+ A24-restricted **cytotoxic T lymphocytes**. Dai L C; West K; Littaua R; Takahashi K; Ennis F A. (Department of Medicine, University of Massachusetts Medical Center, Worcester 01655.) Journal of virology, (1992 May) 66 (5) 3151-4. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB A human leukocyte antigen A24-restricted **CD8**+ **cytotoxic T-cell** clone specific for gp41 of **human immunodeficiency virus** type 1 was isolated from an infected individual. The epitope was localized to amino acids 584 to 591 (YLKDQQLL, NL43 env sequence) of gp41 by using a panel of recombinant vaccinia viruses that contain truncated env genes and synthetic peptides. The clone killed autologous B-lymphoblastoid cell lines pulsed with a synthetic peptide reflecting the sequence of the IIIB and MN strains. This clone, however, **failed** to kill target cells pulsed with the peptides that have a mutation from Lys to Arg or Gln at amino acid 585 which is present in some prototype **human immunodeficiency virus** type 1 strains, e.g., ADA, JFL, SC, ALA1, BAL1, SF2, VRF, SF33, and WMJ2. This finding that a mutation at amino acid 585 on gp41 results in nonrecognition by human leukocyte antigen A24-restricted **CD8**+ **cytotoxic T lymphocytes** suggests that antigenic variation at T-cell epitopes contributes to the **failure** of immune control of **human immunodeficiency virus** type 1 infections.

L47 ANSWER 243 OF 289 MEDLINE on STN
93292186. PubMed ID: 8099857. T cell receptor V beta repertoire in **HIV**-infection individuals: lack of evidence for selective V beta deletion. Boyer V; Smith L R; Ferre F; Pezzoli P; Trauger R J; Jensen F C; Carlo D J. (Immune Response Corporation, Carlsbad, CA 92008.) Clinical and experimental immunology, (1993 Jun) 92 (3) 437-41. Journal code: 0057202. ISSN: 0009-9104. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The gradual decline of CD4+ T lymphocytes in **HIV** infected individuals culminates in the lethal immunosuppression of AIDS. The mechanism of CD4+ T cell loss is currently unknown, but has recently been suggested to occur as a result of an **HIV**-encoded superantigen which facilitates a selective deletion of T cells expressing specific V beta genes. To verify and extend such observations, peripheral blood leucocytes (PBL) from 15 **HIV**+ individuals, 10 of which had very low CD4 T cell counts (< 200/mm3), were analysed for T cell receptor (TCR) V beta gene expression. In contrast to a recent study, the results presented here **fail** to provide evidence that selective loss of V beta-bearing T cells occurs in **HIV**+ individuals. Furthermore, when PBL from **HIV**+ individuals were stimulated with Staphylococcal enterotoxin B (SEB), T cells expressing V beta subfamilies known to engage this superantigen were expanded, indicating that such cells were not deleted and were responsive to stimulation by a bacterial superantigen. Collectively, these data suggest that CD4 loss in **HIV** patients does not occur in a V beta-selective, superantigen-mediated fashion.

L47 ANSWER 242 OF 289 MEDLINE on STN
93305206. PubMed ID: 8318170. Lymphocyte activation in **HIV**-1 infection. I. Predominant proliferative defects among CD45R0+ cells of the CD4 and **CD8** lineages. Janossy G; Borthwick N; Lomnitzer R; Medina E; Squire S B; Phillips A N; Lipman M; Johnson M A; Lee C; Bofill M. (Department of Clinical Immunology, Royal Free Hospital and School of Medicine, London, UK.) AIDS (London, England), (1993 May) 7 (5) 613-24. Journal code: 8710219. ISSN: 0269-9370. Pub. country: United States. Language: English.

AB OBJECTIVES AND DESIGN: The proliferative defects of CD4 and **CD8** cells taken from 474 **HIV**-1-seropositive individuals during various stages of disease were quantitated. Phytohaemagglutinin (PHA) and soluble anti-CD3 were used in optimal mitogenic concentrations in the presence of recombinant interleukin-2 (rIL-2) and conditioned medium, and the proliferation of cells from **HIV**-1-seropositive donors was assessed in co-culture with **HIV**-1-seronegative cells in order to exclude effects of cytokine deficiency. Defects within the CD45RA+ ('unprimed') and CD45R0+ ('primed') T-cell populations were also investigated. METHODS: Quantitative immunofluorescence and double and triple labelling in flow cytometry were performed for (1) CD25 (IL-2 receptor alpha chain) expression, (2) lymphocyte and T-cell survival, and (3) blast transformation and proliferation--in relation to the original input of cells for each subpopulation. RESULTS: T cells from normal and **HIV**-1-seropositive donors were CD25+ at day 1. In **HIV**-1-seropositive patients a variable number of CD4 and **CD8** lymphocytes **failed** to further increase CD25, and died as a sign of activation-associated lymphocyte death (AALD). Forty-two per cent of asymptomatic subjects, including 32% of those with CD4 cell counts > 400 x 10(6)/l, showed a poor blast transformation (< 30% blasts). Cells from **HIV**-1-seropositive donors showed poor blast responses when co-cultured with **HIV**-1-seronegative cells; both CD4 and **CD8** cells were handicapped. In asymptomatic **HIV**-1-seropositive people T cells with the CD45R0+ RA- ('primed') phenotype were three to five times more vulnerable to AALD than the CD45RA+ RO- ('unprimed') cells. In patients in Centers for Disease Control and Prevention (CDC) disease stage IV both CD45R0+ and -RA+ populations were severely affected. CONCLUSIONS: This is the first quantitative analysis to demonstrate that in **HIV**-1 infection mitogen-stimulated CD45R0+ ('primed') T cells preferentially die upon activation. Both the CD4 and **CD8** lineages are affected, as seen in animal models of graft versus host disease. AALD may explain defects of immunological memory. The analysis of AALD may be a suitable assay for studying whether antiviral drugs influence the proliferative responses of lymphocytes.

L47 ANSWER 236 OF 289 MEDLINE on STN
94255016. PubMed ID: 7515165. **Cytotoxic T-cell** activity antagonized by naturally occurring **HIV**-1 Gag variants. Klenerman P; Rowland-Jones S; McAdam S; Edwards J; Daenke S; Lalloo D; Koppe B; Rosenberg W; Boyd D; Edwards A; +. (Nuffield Department of Clinical Medicine, University of

Oxford, UK.) Nature, (1994 Jun 2) 369 (6479) 403-7. Journal code: 0410462. ISSN: 0028-0836. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Most asymptomatic individuals infected with **HIV**-1 have a **cytotoxic T lymphocyte** (**CTL**) response to the virus Gag proteins which can be demonstrated in vitro. Epitopes have been mapped in p17 Gag and p24 Gag restricted by HLA-B8 (p17-3 and p24-13) and -B27 (p24-14). Viruses isolated from patients who make **CTL** responses to these peptides vary within the genetic sequences encoding these epitopes and some mutations lead to reduction in killing activity in vitro. This was attributed to either **failure** of the variant epitope to bind major histocompatibility complex class I or **failure** of T-cell receptors to bind the presented peptide. But peptide variants of class I-restricted epitopes cause 'antagonism', that is, the presence of a variant epitope (in the form of peptide) inhibits normal lysis of targets presenting the original epitope. This mirrors similar findings in class II-restricted systems. Here we report that naturally occurring variant forms of p17-3, p24-13 and p24-14 may cause antagonism of **CTL** lines derived from the same individuals. The effect is present if the epitopes are derived from synthetic peptides and when they are processed from full-length proteins expressed by either recombinant vaccinia constructs or replicating **HIV**.

L47 ANSWER 226 OF 289 MEDLINE on STN
95104273. PubMed ID: 7805718. Dysregulation of interleukin-7 receptor may generate loss of **cytotoxic T cell** response in **human immunodeficiency virus** type 1 infection. Carini C; McLane M F; Mayer K H; Essex M. (Department of Cancer Biology, Harvard School of Public Health, Boston, MA 02115.) European journal of immunology, (1994 Dec) 24 (12) 2927-34. Journal code: 1273201. ISSN: 0014-2980. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB Virus-specific **cytotoxic T lymphocytes** (**CTL**) play a crucial role in modulating an immune response against human immunodeficiency type 1 (**HIV**-1) infection. The generation of effector cytotoxic cells from **CTL** precursors involves intricate interactions with antigen via T cell receptors (TcR) and soluble cytokines. Interleukin (IL)-7 can affect T cell maturation and differentiation. Here we report on a group of five **HIV**-1-positive individuals who tested negative for env- and gag-specific **CTL** activity. When exogenous recombinant human IL-7 was added as a stimulus to the cultures, none (0/5) of the **CTL**-negative individuals exhibited a **CTL** response. Individuals that were negative for **HIV**-1-specific **CTL** activity were found to lack IL-7 receptor (IL-7R) on **CD8**+ cells with a comparable reduction on CD4+ cells. Increased shedding of IL-7R in the culture supernatant was observed. A significant reduction in receptor number was detected by binding of 125I-labeled IL-7 and Scatchard analysis. The lack of IL-7R is probably not due to endogenous IL-7, since it was not detectable in the culture supernatants of the patients studied. **HIV**-1 proteins may cause down-modulation of IL-7R expression, either by producing an insufficient number of molecules or by rapid decay of IL-7R on T cells. These changes may alter the cells' capability to respond to the IL-7 growth signal, resulting in **CTL** **failure** and subsequent mishandling of the virus.

L47 ANSWER 154 OF 289 MEDLINE on STN
1999101466. PubMed ID: 9886375. A single specific amino acid residue in peptide antigens is sufficient to activate memory **CTL**: potential role of cross-reactive peptides in memory T cell maintenance. Reali E; Guerrini R; Marastoni M; Tomatis R; Masucci M G; Traniello S; Gavioli R. (Department of Biochemistry and Molecular Biology, University of Ferrara, Italy.. reali.eva@hsr.it) . Journal of immunology (Baltimore, Md. : 1950), (1999 Jan 1) 162 (1) 106-13. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB In the present study, we examined the structural requirements of peptide Ags for productive interactions with the TCR of **CTL**. For this purpose, we used as a model a previously identified immunodominant epitope that represents the target of EBV-specific HLA-A11-restricted **CTL** responses. By the use of peptides having minimal sequence homology with the wild-type

epitope, we demonstrated that it is possible to selectively expand and reactivate memory **CTL** precursors without triggering the lytic mechanisms of wild-type specific effectors. In fact, stimulation of PBL from EBV-seropositive donors by polyalanine analogues, sharing only the putative TCR contact residue with the natural epitope, exclusively induced clonal expansion and reactivation of EBV-specific memory **CTL** precursors. Interestingly, these polyalanine peptides **failed** to trigger the cytotoxic function of CTLs specific for the wild-type viral epitope. This clearly indicates that reactivation of memory **CTL** precursors and triggering of the cytotoxic function have different requirements. The same phenomenon was observed using as stimulators naturally occurring peptides carrying the appropriate TCR contact residue. These data strongly suggest that cross-reactive peptides may play an important role in the expansion and reactivation of **CTL** clones from the memory T cell pool, and may be involved in long-term maintenance of T cell memory.

L47 ANSWER 203 OF 289 MEDLINE on STN
96391803. PubMed ID: 8794018. Evolution and plasticity of **CTL** responses against **HIV**. Autran B; Hadida F; Haas G. (Laboratoire d'Immunologie Cellulaire et Tissulaire, CNRS URA 625, CH Pitie-Salpetriere 83, de I'hopital, Batiment CERVI, 75013 Paris, France.) Current opinion in immunology, (1996 Aug) 8 (4) 546-53. Ref: 71. Journal code: 8900118. ISSN: 0952-7915. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Exceptionally potent **cytotoxic T lymphocyte** responses are generated after **HIV** invasion and probably control the primary infection as well as the asymptomatic phase of **HIV** infection. The chronic phase appears as a quasi-equilibrium between waves of new **HIV** variants and variant-specific CTLs, thus sustaining continuous **CTL** activation which eventually **fails** to eradicate **HIV** disease progression and the reascension of viral replication. Meanwhile, both the host and the virus develop various strategies either to stop or to evade this potentially deleterious permanent **CTL** activity. The transient effectiveness of CTLs opens perspectives for understanding disease progression generally as well as for immune therapeutic strategies.

L47 ANSWER 90 OF 289 MEDLINE on STN
2001207126. PubMed ID: 11242192. Evidence of productively infected **CD8**+ T cells in patients with AIDS: implications for **HIV**-1 pathogenesis. Saha K; Zhang J; Zerhouni B. (Children's Research Institute, Department of Pediatrics and Molecular Virology, Immunology, & Medical Genetics, The Ohio State University Medical Center, Columbus, Ohio 43205-2696, USA.. sahak@pediatrics.ohio-state.edu) . Journal of acquired immune deficiency syndromes (1999), (2001 Mar 1) 26 (3) 199-207. Journal code: 100892005. ISSN: 1525-4135. Pub. country: United States. Language: English.

AB **CD8**+ T lymphocytes play an important protective role against **HIV** infection. The onset of AIDS is associated with a decline in both the number of **CD8**+ T lymphocytes and anti-**HIV** cytotoxic activity in **CD8**+ T cells. The reason for this progressive **failure** of **CD8**+ T cells in **HIV**-1 infection remains unknown. Earlier reports have shown presence of viral DNA in **CD8**+ cells of **HIV**-1-infected patients; under some conditions, **CD8**+ T cells have been shown to express CD4 in vitro and can be susceptible to infection with **HIV**-1. However, whether **CD8**+ lymphocytes in vivo can be productively infected with **HIV**-1 remains unclear. In this study, we generated multiple **CD8**+ T-cell clones from two patients with AIDS. These clones were **CD8**+/CD3+ but did not express CD4. Several of these **CD8**+ clones from both patients were found to be endogenously infected with **HIV**-1 and spontaneously produced these viruses. **CD8**+ cell-produced **HIV**-1 was biologically competent because viruses produced by most of these clones could efficiently infect and replicate in peripheral blood lymphocytes from **HIV**-negative donors. In addition, some of these viruses were able to form syncytia in MT-2 cells indicating syncytium-inducing phenotype. Comparison of the sequences in V3 loop areas among different viruses showed changes in some of the clones from both patients. For the first time, this report provides direct evidence that mature **CD8**+ T cells can be productively infected with **HIV**-1 in patients with AIDS. Direct infection of **CD8**+ T lymphocytes

may play a role in the eventual failure of these cells in HIV 1 infection.

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     (FILE 'HOME' ENTERED AT 19:42:02 ON 01 APR 2004)

     FILE 'USPATFULL' ENTERED AT 19:42:32 ON 01 APR 2004
                E FRANCHINI GENOVEFFA/IN
L1            7 S E3
L2            0 S ZDENEK HEL/IN
                E ZDENEK HEL/IN
L3            0 S HEL ZDENEK/IN S HEL ZDENEK/IN
L4            0 S GENE SHEARER/IN
L5            1 S SHEARER GENE/IN
                E SHEARER GENE/IN
L6            7 S E4
                E NACSA JANOS/IN

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L7          196 S E3 OR E4
L8           67 S L7 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L9           16 S L8 AND (MHC OR MAJOR HISTOCOMPATIBILITY OR CTL OR CYTOTOXIC T
L10           0 S HEL Z/AU S HEL Z/AU
                E SHEARER G M/AU
L11         358 S E3 OR E6 OR E7
L12         118 S L11 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L13          20 S L12 AND (MAJOR HISTOCOMPATIBILITY OR CTL OR CYTOTOXIC)
                E NACSA J/AU
L14          22 S E3 OR E4

     FILE 'WPIDS' ENTERED AT 20:01:20 ON 01 APR 2004
                E FRANCHINI G/IN
L15          18 S E3
L16          10 S L15 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
                E SHEARER G M/IN
L17          10 S E3
L18          15 S E3 OR E2
                E NACSA J/IN
L19           3 S E3

     FILE 'USPATFULL' ENTERED AT 20:09:31 ON 01 APR 2004
L20       31746 S (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L21       10927 S L20 AND (CTL OR CYTOTOXIC)
L22        1761 S L21 AND (HIV/CLM OR HUMAN IMMUNODEFICIENCY VIRUS/CLM)
L23         233 S L22 AND (CTL/CLM OR CYTOTOXIC/CLM)
L24         186 S L23 AND (VACCIN? OR IMMUNOGEN?)
L25         182 S L24 AND (PROTECT? OR PREVENT?)
L26          96 S L25 AND (DNA/CLM OR NUCLEIC ACID/CLM)
L27          33 S L26 AND AY<2000
L28           1 S US6656471/PN
L29           1 S US6319666/PN

     FILE 'MEDLINE' ENTERED AT 20:22:25 ON 01 APR 2004
L30      139974 S (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L31        5709 S L30 AND (CTL OR CYTOTOXIC T CELL? OR CYTOTOXIC T LYMPHOCYTE?
L32         176 S L31 AND (ESCAPE OR EVASION)
L33          78 S L32 AND (VACCIN? OR PREVENT? OR THERAP?)
L34          98 S L32 NOT L33
                E KOENIG M/AU
L35         107 S E3
L36           1 S L35 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L37         122 S E4-E12
                E E12
L38          46 S E1-E12
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          E E12
L39          36 S E1-E12
L40         184 S L37 OR L38 OR L39
L41           2 S L40 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L42        9232 S L30 AND PY=1995
L43         407 S L42 AND (CTL OR CYTOTOXIC T LYMPHOCYTE? OR CYTOTOXIC T CELL?
L44          95 S L43 AND (THERAPY OR IMMUNOTHERAPY OR ADOPTIVE)
L45          92 S L44 NOT L32
L46         310 S L31 AND (FAIL?)
L47         289 S L46 NOT L32

=> e koenig s/au
E1            2      KOENIG RONALD J/AU
E2            2      KOENIG ROY/AU
E3          103 --> KOENIG S/AU
E4           44      KOENIG S B/AU
E5           26      KOENIG S C/AU
E6            4      KOENIG S E/AU
E7          118      KOENIG S H/AU
E8            1      KOENIG S L/AU
E9            7      KOENIG S M/AU
E10           2      KOENIG S P/AU
E11           1      KOENIG SCOTT/AU
E12           1      KOENIG SERENA/AU

=> s e3
L48         103 "KOENIG S"/AU

=> s l48 and (HIV or human immunodeficiency virus)
        135256 HIV
       8464764 HUMAN
        112466 IMMUNODEFICIENCY
        372233 VIRUS
         42485 HUMAN IMMUNODEFICIENCY VIRUS
                 (HUMAN(W)IMMUNODEFICIENCY(W)VIRUS)
L49          33 L48 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)

=> d l49,cbib,1-33
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L49 ANSWER 1 OF 33 MEDLINE on STN
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     FILE 'USPATFULL' ENTERED AT 19:42:32 ON 01 APR 2004
                E FRANCHINI GENOVEFFA/IN
L1            7 S E3
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                E ZDENEK HEL/IN
L3            0 S HEL ZDENEK/IN S HEL ZDENEK/IN
L4            0 S GENE SHEARER/IN
L5            1 S SHEARER GENE/IN
                E SHEARER GENE/IN
L6            7 S E4
                E NACSA JANOS/IN

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L7          196 S E3 OR E4
L8           67 S L7 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L9           16 S L8 AND (MHC OR MAJOR HISTOCOMPATIBILITY OR CTL OR CYTOTOXIC T
L10           0 S HEL Z/AU S HEL Z/AU
                E SHEARER G M/AU
L11         358 S E3 OR E6 OR E7
L12         118 S L11 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L13          20 S L12 AND (MAJOR HISTOCOMPATIBILITY OR CTL OR CYTOTOXIC)
                E NACSA J/AU
L14          22 S E3 OR E4

     FILE 'WPIDS' ENTERED AT 20:01:20 ON 01 APR 2004
                E FRANCHINI G/IN
L15          18 S E3
L16          10 S L15 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
                E SHEARER G M/IN
L17          10 S E3
L18          15 S E3 OR E2
                E NACSA J/IN
L19           3 S E3

     FILE 'USPATFULL' ENTERED AT 20:09:31 ON 01 APR 2004
L20       31746 S (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L21       10927 S L20 AND (CTL OR CYTOTOXIC)
L22        1761 S L21 AND (HIV/CLM OR HUMAN IMMUNODEFICIENCY VIRUS/CLM)
L23         233 S L22 AND (CTL/CLM OR CYTOTOXIC/CLM)
L24         186 S L23 AND (VACCIN? OR IMMUNOGEN?)
L25         182 S L24 AND (PROTECT? OR PREVENT?)
L26          96 S L25 AND (DNA/CLM OR NUCLEIC ACID/CLM)
L27          33 S L26 AND AY<2000
L28           1 S US6656471/PN
L29           1 S US6319666/PN

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L30      139974 S (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L31        5709 S L30 AND (CTL OR CYTOTOXIC T CELL? OR CYTOTOXIC T LYMPHOCYTE?
L32         176 S L31 AND (ESCAPE OR EVASION)
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L33             78 S L32 AND (VACCIN? OR PREVENT? OR THERAP?)
L34             98 S L32 NOT L33
                   E KOENIG M/AU
L35            107 S E3
L36              1 S L35 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L37            122 S E4-E12
                   E E12
L38             46 S E1-E12
                   E E12
L39             36 S E1-E12
L40            184 S L37 OR L38 OR L39
L41              2 S L40 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L42           9232 S L30 AND PY=1995
L43            407 S L42 AND (CTL OR CYTOTOXIC T LYMPHOCYTE? OR CYTOTOXIC T CELL?
L44             95 S L43 AND (THERAPY OR IMMUNOTHERAPY OR ADOPTIVE)
L45             92 S L44 NOT L32
L46            310 S L31 AND (FAIL?)
L47            289 S L46 NOT L32
                   E KOENIG S/AU
L48            103 S E3
L49             33 S L48 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)

=> s l31 and (avidity or affinity or titer)
          3410 AVIDITY
        181875 AFFINITY
         19735 TITER
L50          151 L31 AND (AVIDITY OR AFFINITY OR TITER)

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L51          135 L50 NOT (L32 OR L47)

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L51 ANSWER 135 OF 135 MEDLINE on STN
88009083. PubMed ID: 3498755. Antibody-dependent cellular cytotoxicity-inducing antibodies against **human immunodeficiency virus**. Presence at different clinical stages. Ljunggren K; Bottiger B; Biberfeld G; Karlson A; Fenyo E M; Jondal M. (Department of Immunology, Karolinska Institute, Stockholm, Sweden.) Journal of immunology (Baltimore, Md. : 1950), (1987 Oct 1) 139 (7) 2263-7. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

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L51 ANSWER 3 OF 135 MEDLINE on STN
2004153034. PubMed ID: 15046253. Molecular mechanisms and biological significance of **CTL avidity**. Snyder James T; Alexander-Miller Martha A; Berzofskyl Jay A; Belyakov Igor M. (Molecular Immunogenetics and Vaccine Research Section, Metabolism Branch, National Cancer Institute, NIH, Bethesda, MD 20892, USA.) Curr HIV Res, (2003 Jul) 1 (3) 287-94. Journal code: 101156990. ISSN: 1570-162X. Pub. country: Netherlands. Language: English.

AB **CD8** CTLs are a major effector for protection against cancer as well as many infectious diseases, including **HIV**/AIDS. **CD8 CTL** recognize antigenic peptides in the context of class I MHC. **CTL** functional **avidity** has been shown to be an important determinant of in vivo efficacy. **CTL** that can recognize peptide/MHC only at high antigen density are termed low **avidity CTL**, while those that can recognize their cognate antigen at low densities are termed high **avidity CTL**. Recent studies have demonstrated that high **avidity** CTLs are essential for the effective clearance of viral infections and for the elimination of

tumor cells. At this time, approaches that can target high **avidity** cells for expansion in vivo are not well defined; however, new insights are beginning to emerge. A recent study has shown that prime-boost immunization may be an effective method to generate high **avidity** CTLs that recognize **HIV** antigens. In addition, we recently found that high levels of costimulation (signal 2) can skew the **CTL** response toward higher **avidity** cells. Thus, vectors expressing a triad of costimulatory molecules (TRICOM) or dendritic cells expressing higher levels of costimulatory molecules, can be used to induce high **avidity CTL**. Finally a critical role for CD4+ T cell help in the generation of high **avidity** cells has recently been identified (Palmer, manuscript submitted). While high **avidity** CTLs are superior for viral and tumor clearance, they also have a greater sensitivity to antigen induced cell death. In some types of chronic infections, such as **HIV** and HCV, as well as in cancer, the host may lose, by clonal exhaustion or other apoptotic mechanisms, the effector cells that are most critical to viral or tumor clearance. In this review, we examine the current knowledge concerning **CTL avidity**. We discuss the factors that may distinguish high **avidity** CTLs from low **avidity** CTLs and describe some of the mechanisms these cells use to clear viral infections. In addition, we study possible immunization strategies that may be used to elicit higher **avidity** CTLs and describe what is known about the factors that render these cells more susceptible to apoptosis than low **avidity** CTLs. Finally, we will incorporate these various elements into a general discussion of possible approaches for induction and maintenance of an effective immune response that can result in clearance of tumors or chronic viral infections and the relevance to vaccine development.

L51 ANSWER 4 OF 135 MEDLINE on STN
2004149985. PubMed ID: 15043207. T cell immunity to **HIV**: defining parameters of protection. Maecker Holden T; Maino Vernon C. (BD Biosciences, Immunocytometry Systems, 2350 Qume Drive, San Jose, CA 95131, USA.. holden_maecker@bd.com) . Curr HIV Res, (2003 Apr) 1 (2) 249-59. Journal code: 101156990. ISSN: 1570-162X. Pub. country: Netherlands. Language: English.

AB In recent years, CD4 and **CD8** T cell responses to **HIV** and SIV infection have been increasingly measured with the use of single-cell assays such as ELISPOT, MHC-peptide oligomers, and cytokine flow cytometry. The results of these assays have been compared to those obtained with traditional bulk assays such as lymphoproliferation (by 3H-thymidine incorporation) and cytotoxicity (by 51Cr release). Such comparisons have led to some general understanding of the T cell responses that characterize progressive disease, long-term non-progressors, and individuals with viral suppression achieved by anti-retroviral therapy. In addition, prophylactic and therapeutic vaccine trials have also begun to use these assays of T cell immunity to gauge the immunogenicity of the vaccines. Whether such analyses will allow us to pick the best vaccine constructs, and whether they will provide us with an improved understanding of what constitutes protective cellular immunity to **HIV**, are major questions for the field. These questions will be examined in this review from the standpoint of current data and comparisons to other viral diseases. It is hypothesized that sophisticated multiparametric assays will be required to sort out the factors relevant for protective immunity in this complex disease. These parameters may include functional **avidity**, epitope breadth and specificity, proliferative capacity, cytokine repertoire, degree of anergy, and differentiation phenotype, as well as magnitude, of **HIV**-specific CD4 and **CD8** T cells.

L51 ANSWER 10 OF 135 MEDLINE on STN
2003464460. PubMed ID: 14500671. Impacts of **avidity** and specificity on the antiviral efficiency of **HIV**-1-specific **CTL**. Yang Otto O; Sarkis Phuong T Nguyen; Trocha Alicja; Kalams Spyros A; Johnson R Paul; Walker Bruce D. (Division of Infectious Diseases and AIDS Institute, University of California, Los Angeles Medical Center, Los Angeles, CA 90095, USA.. oyang@mednet.ucla.edu) . Journal of immunology (Baltimore, Md. : 1950), (2003 Oct 1) 171 (7) 3718-24. Journal code: 2985117R. ISSN: 0022-1767.

Pub. Country: United States. Language: English.

AB Although **CD8**(+) CTLs are presumed to be an important mediator of protective immunity in **HIV**-1 infection, the factors that determine **CTL** antiviral efficiency are poorly understood. Two factors that have been proposed to influence **CTL** antiviral function are antigenic **avidity** and epitope specificity. In this study we evaluate these by examining the activity of **HIV**-1-specific **CTL** against acutely infected cells. The ability of **CTL** to kill infected cells is variable and depends more on epitope specificity than functional **avidity** within the range for the tested clones (50% of maximal killing, 50 pg/ml to 100 ng/ml); killing efficiency is similar for different clones recognizing the same epitope, despite their variation in **avidity**. When **CTL** clones are tested for their ability to suppress viral replication, similar results are observed. Inhibition is more dependent on epitope specificity than functional **avidity** among the tested clones (50% of maximal killing, 20 pg/ml to 20 ng/ml). Thus, **CTL** specificity can be an overriding factor in the ability of **CTL** to interact with **HIV**-1-infected cells, indicating that factors determining the process of epitope presentation on infected cells have a key influence on **CTL** efficiency. These results suggest that **CTL** specificity may have a pivotal role in the immunopathogenesis of infection, and that simple quantitative measures of **CTL** may be insufficient indicators of the **CTL** response to **HIV**-1.

L51 ANSWER 11 OF 135 MEDLINE on STN

2003425947. PubMed ID: 12965025. The race between initial T-helper expansion and virus growth upon **HIV** infection influences polyclonality of the response and viral set-point. Korthals Altes H; Ribeiro R M; de Boer R J. (Laboratoire d'Immunologie Cellulaire et Tissulaire, Hopital Pitie-Salpetriere, 91 Boulevard de l'Hopital, 75013 Paris, France.. altes@science.uva.nl) . Proceedings of the Royal Society of London. Series B. Biological sciences, (2003 Jul 7) 270 (1522) 1349-58. Journal code: 7505889. ISSN: 0962-8452. Pub. country: England: United Kingdom. Language: English.

AB Infection with **HIV** is characterized by very diverse disease-progression patterns across patients, associated with a wide variation in viral set-points. Progression is a multifactorial process, but an important role has been attributed to the **HIV**-specific T-cell response. To explore the conditions under which different set-points may be explained by differences in initial CD4 and **CD8** T-cell responses and virus inoculum, we have formulated a model assuming that **HIV**-specific CD4 cells are both targets for infection and mediators of a monoclonal or polyclonal immune response. Clones differ in functional **avidity** for **HIV** epitopes. Importantly, in contrast to previous models, in this model we obtained coexistence of multiple clones at steady-state viral set-point, as seen in **HIV** infection. We found that, for certain parameter conditions, multiple steady states are possible: with few initial CD4 helper cells and high virus inoculum, no immune response is established and target-cell-limited infection follows, with associated high viral load; when CD4 clones are initially large and virus inoculum is low, infection can be controlled by several clones. The conditions for the dependence of viral set-point on initial inoculum and CD4 T-helper clone availability are investigated in terms of the effector mechanism of the clones involved.

L51 ANSWER 13 OF 135 MEDLINE on STN

2003419110. PubMed ID: 12917462. Optimization and immune recognition of multiple novel conserved HLA-A2, **human immunodeficiency virus** type 1-specific **CTL** epitopes. Corbet Sylvie; Nielsen Henrik Vedel; Vinner Lasse; Lauemoller Sanne; Therrien Dominic; Tang Sheila; Kronborg Gitte; Mathiesen Lars; Chaplin Paul; Brunak Soren; Buus Soren; Fomsgaard Anders. (Department of Virology, Statens Serum Institut, 5 Artillerivej, DK-2300 Copenhagen S, Denmark.) Journal of general virology, (2003 Sep) 84 (Pt 9) 2409-21. Journal code: 0077340. ISSN: 0022-1317. Pub. country: England: United Kingdom. Language: English.

AB MHC-I-restricted cytotoxic responses are considered a critical component of protective immunity against viruses, including **human**

immunodeficiency virus type 1 (**HIV**-1). CTLs directed against accessory and early regulatory **HIV**-1 proteins might be particularly effective; however, **CTL** epitopes in these proteins are rarely found. Novel artificial neural networks (ANNs) were used to quantitatively predict HLA-A2-binding **CTL** epitope peptides from publicly available full-length **HIV**-1 protein sequences. Epitopes were selected based on their novelty, predicted HLA-A2-binding **affinity** and conservation among **HIV**-1 strains. HLA-A2 binding was validated experimentally and binders were tested for their ability to induce **CTL** and IFN-gamma responses. About 69 % were immunogenic in HLA-A2 transgenic mice and 61 % were recognized by **CD8**(+) T-cells from 17 HLA-A2 **HIV**-1-positive patients. Thus, 31 novel conserved **CTL** epitopes were identified in eight **HIV**-1 proteins, including the first HLA-A2 minimal epitopes ever reported in the accessory and regulatory proteins Vif, Vpu and Rev. Interestingly, intermediate-binding peptides of low or no immunogenicity (i.e. subdominant epitopes) were found to be antigenic and more conserved. Such epitope peptides were anchor-optimized to improve immunogenicity and further increase the number of potential vaccine epitopes. About 67 % of anchor-optimized vaccine epitopes induced immune responses against the corresponding non-immunogenic naturally occurring epitopes. This study demonstrates the potency of ANNs for identifying putative virus **CTL** epitopes, and the new **HIV**-1 **CTL** epitopes identified should have significant implications for **HIV**-1 vaccine development. As a novel vaccine approach, it is proposed to increase the coverage of **HIV** variants by including multiple anchor-optimized variants of the more conserved subdominant epitopes.

L51 ANSWER 45 OF 135 MEDLINE on STN
2001212279. PubMed ID: 11160212. High-**avidity** **CTL** exploit two complementary mechanisms to provide better protection against viral infection than low-**avidity** **CTL**. Derby M; Alexander-Miller M; Tse R; Berzofsky J. (Molecular Immunogenetics and Vaccine Research Section, Metabolism Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892-1578, USA.) Journal of immunology (Baltimore, Md. : 1950), (2001 Feb 1) 166 (3) 1690-7. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB Previously, we observed that high-**avidity** **CTL** are much more effective in vivo than low-**avidity** **CTL** in elimination of infected cells, but the mechanisms behind their superior activity remained unclear. In this study, we identify two complementary mechanisms: 1) high-**avidity** **CTL** lyse infected cells earlier in the course of a viral infection by recognizing lower Ag densities than those distinguished by low-**avidity** **CTL** and 2) they initiate lysis of target cells more rapidly at any given Ag density. Alternative mechanisms were excluded, including: 1) the possibility that low-**avidity** **CTL** might control virus given more time (virus levels remained as high at 6 days following transfer as at 3 days) and 2) that differences in efficacy might be correlated with homing ability. Furthermore, adoptive transfer of high- and low-**avidity** **CTL** into SCID mice demonstrated that transfer of a 10-fold greater amount of low-**avidity** **CTL** could only partially compensate for their decreased ability to eliminate infected cells. Thus, we conclude that high-**avidity** **CTL** exploit two complementary mechanisms that combine to prevent the spread of virus within the animal: earlier recognition of infected cells when little viral protein has been made and more rapid lysis of infected cells.

L51 ANSWER 64 OF 135 MEDLINE on STN
1999100990. PubMed ID: 9885899. The effect of epitope variation on the profile of **cytotoxic T lymphocyte** responses to the **HIV** envelope glycoprotein. Kmieciak D; Bednarek I; Takiguchi M; Wasik T J; Bratosiewicz J; Wierzbicki A; Teppler H; Pientka J; Hsu S H; Kaneko Y; Kozbor D. (Center for Neurovirology, Department of Neurology, Allegheny University of the Health Sciences, Philadelphia, PA 19102, USA.) International immunology, (1998 Dec) 10 (12) 1789-99. Journal code: 8916182. ISSN: 0953-8178. Pub. country: ENGLAND: United Kingdom. Language: English.

AB To address the relationship between viral and host factors during **HIV**

infection, we analyzed the effect of viral mutations on T cell responses in seropositive, asymptomatic HLA-A2+ individuals using four envelope (env)-specific peptides with the HLA-A*0201 binding motif. We showed that the natural sequence variation was frequent within epitopes located in the C-terminal region of the env glycoprotein and was largely responsible for a lower env-specific **cytotoxic T lymphocyte** (**CTL**) activity in the peptide-stimulated cultures. The highest **CTL** responses in vitro were induced with conserved epitopes D1 and 4.3 that mapped to the N-terminal region of the env glycoprotein. These peptides exhibited high binding **affinity** for HLA-A*0201 molecules and stimulated **CD8+** T cells of relatively limited TCR Vbeta chain repertoire. Decreased **CTL** activities to the D1 epitope were observed in the absence of any detectable viral mutation, and were associated with lower proliferative responses and expression of the CD28 antigen. Results of this study demonstrate that the degree of sequence variation within a stimulatory epitope of the viral quasispecies, as well as proliferative potential of the effector cells, are among the factors underlying decreased **CTL** activity in **HIV**-infected patients. These experiments also provide evidence that the D1 peptide might be useful for the development of vaccines and immune-based therapy.

L51 ANSWER 68 OF 135 MEDLINE on STN
1998418500. PubMed ID: 9747728. Characterization of HLA-B57-restricted **human immunodeficiency virus** type 1 Gag- and RT-specific **cytotoxic T lymphocyte** responses. Klein M R; van der Burg S H; Hovenkamp E; Holwerda A M; Drijfhout J W; Melief C J; Miedema F. (Department of Clinical Viro-Immunology, Central Laboratory of the Netherlands Red Cross Blood Transfusion Service, and University of Amsterdam.) Journal of general virology, (1998 Sep) 79 (Pt 9) 2191-201. Journal code: 0077340. ISSN: 0022-1317. Pub. country: ENGLAND: United Kingdom. Language: English.

AB HLA-B57 has been shown to be strongly associated with slow disease progression in **human immunodeficiency virus** type 1 (**HIV**-1)-infected patients from the Amsterdam Cohort. Since **HIV**-1-specific **CTL** can control and eliminate virus-infected cells, we sought to characterize the dominant HLA-B57-restricted **CTL** responses at the epitope level. It was found that HLA-B57-restricted **CTL** responses were targeted at multiple proteins of **HIV**-1, with **CTL** specific for Gag and RT being the most pronounced. Gag-specific **CTL** recognized peptides ISPRTLNAW (aa 147-155) and STLQEQIGW (aa 241-249), which had previously been reported as HLA-B57-restricted. The RT-specific **CTL** response in one long-term survivor studied in great detail persisted for > 10 years and was dominated by HLA-B57-restricted **CTL** that recognized the newly defined epitope IVLPEKDSW (RT(LAI), aa 244-252). This epitope could be recognized in the context of both HLA-B*5701 and HLA-B*5801. Interestingly, three epitope variants of IVLPEKDSW were observed, which coincided with the strongest detectable **CTL** response to RT. One variant (T2E7) was not recognized by IVLPEKDSW-specific **CTL** despite the fact that this variant bound to HLA-B*5701 with a similar **affinity** as the index peptide. Finally, only viruses which contained the epitope index sequence were obtained suggesting efficient virus control by **CTL**. In conclusion, we report the characterization of dominant **HIV**-1 Gag- and RT-derived, HLA-B57-restricted **CTL** epitopes which are associated with longer time to AIDS. Further characterization of **CTL** responses restricted by HLA-B57 and other protective HLA alleles may contribute to the development of effective AIDS vaccines.

L51 ANSWER 71 OF 135 MEDLINE on STN
1998376195. PubMed ID: 9712350. Conversion of a **human immunodeficiency virus cytotoxic T lymphocyte** epitope into a high **affinity** HLA-Cw3 ligand. Zarling A L; Lee D R. (Department of Molecular Microbiology and Immunology, University of Missouri, Columbia 65212, USA.) Human immunology, (1998 Aug) 59 (8) 472-82. Journal code: 8010936. ISSN: 0198-8859. Pub. country: United States. Language: English.

AB To elucidate the residues important for the binding of peptides to HLA-Cw3, a substitutional analysis of two HLA-Cw*0304-binding peptides was performed. The optimal registry and length for a Cw3-restricted epitope

from **HIV** 1 p24gag was determined to be a nonamer, p24gag 144-152. Substituted analogs of this nonamer peptide revealed that substitutions at position 3 (P3) and the carboxyl-terminal P9 were inhibitory to binding, while certain substitutions at the amino-terminal P1 or P2 increased binding significantly. Substituted analogs of another Cw3-restricted peptide, the Cw3 consensus peptide, which binds to HLA-Cw*0304 with a 1,000-fold higher **affinity** and with a greater stability than the **HIV** p24gag nonamer revealed that the P1, P2, P6, and P9 residues play important roles in the ligand's binding to Cw*0304. The incorporation of the amino-terminal P1 and P2 residues from the Cw3 consensus peptide into the **HIV** p24gag 144-152 peptide created a hybrid peptide with profoundly enhanced **affinity** for and stability with Cw*0304. Collectively, these findings provide a clear insight into how peptides interact with HLA-Cw3 and how high **affinity** Cw3 ligands can be constructed.

L51 ANSWER 94 OF 135 MEDLINE on STN
96194537. PubMed ID: 8617954. Immunogenicity of peptides bound to MHC class I molecules depends on the MHC-peptide complex stability. van der Burg S H; Visseren M J; Brandt R M; Kast W M; Melief C J. (Department of Immunohematology and Blood Bank, University Hospital Leiden, The Netherlands.) Journal of immunology (Baltimore, Md. : 1950), (1996 May 1) 156 (9) 3308-14. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB The impact of the MHC class I peptide binding stability on the immunogenicity of particular peptide Ags in class I-restricted **cytotoxic T lymphocyte** responses is not clearly established. Therefore, we have determined the dissociation rate of each peptide from MHC class I at 37 degrees C and compared this to that of a consensus **CTL** epitope. Newly defined immunogenic peptides formed relatively stable MHC-peptide complexes as shown by their low dissociation rates, whereas nonimmunogenic peptides displayed high dissociation rates. In addition virtually all previously described HLA-A*0201-restricted T cell epitopes showed low dissociation rates. Furthermore, we show that the immunogenicity of **HIV**-1-derived peptides can be predicted more accurately by their dissociation rate than by the MHC class I binding **affinity**. Selection of peptides based on **affinity** and their dissociation rate leads to a more precise identification of candidate **CTL** epitopes than selection based on **affinity** alone. These results help to understand why some peptides are recognized by **CTL** and, along with detailed knowledge of protein processing rules, therefore have important implications for the selection of peptides in peptide-based vaccines.

L51 ANSWER 102 OF 135 MEDLINE on STN
95396758. PubMed ID: 7545295. Amino-terminal alteration of the HLA-A*0201-restricted **human immunodeficiency virus** pol peptide increases complex stability and in vitro immunogenicity. Pogue R R; Eron J; Frelinger J A; Matsui M. (Department of Microbiology and Immunology, University of North Carolina, Chapel Hill 27599, USA.) Proceedings of the National Academy of Sciences of the United States of America, (1995 Aug 29) 92 (18) 8166-70. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB Initial studies suggested that major histocompatibility complex class I-restricted viral epitopes could be predicted by the presence of particular residues termed anchors. However, recent studies showed that nonanchor positions of the epitopes are also significant for class I binding and recognition by **cytotoxic T lymphocytes** (CTLs). We investigated if changing nonanchor amino acids could increase class I **affinity**, complex stability, and T-cell recognition of a natural viral epitope. This concept was tested by using the HLA-A 0201-restricted **human immunodeficiency virus** type 1 epitope from reverse transcriptase (pol). Position 1 (P1) amino acid substitutions were emphasized because P1 alterations may not alter the T-cell receptor interaction. The peptide with the P1 substitution of tyrosine for isoleucine (I1Y) showed a binding **affinity** for HLA-A 0201 similar to that of the wild-type pol peptide in a cell lysate assembly assay. Surprisingly, I1Y significantly increased the HLA-A 0201-peptide complex

stability at the cell surface. I1Y sensitized HLA-A 0201 expressing target cells for wild-type pol-specific **CTL** lysis as well as wild-type pol. Peripheral blood lymphocytes from three HLA-A2 **HIV**-seropositive individuals were stimulated in vitro with I1Y and wild-type pol. I1Y stimulated a higher wild-type pol-specific **CTL** response than wild-type pol in all three donors. Thus, I1Y may be an "improved" epitope for use as a **CTL**-based **human immunodeficiency virus** vaccine component. The design of improved epitopes has important ramifications for prophylaxis and therapeutic vaccine development.

L51 ANSWER 105 OF 135 MEDLINE on STN

95363191. PubMed ID: 7543542. Characterization of HLA-A 0201-restricted **cytotoxic T cell** epitopes in conserved regions of the **HIV** type 1 gp160 protein. Dupuis M; Kundu S K; Merigan T C. (Center for AIDS Research, Stanford University, CA 94305, USA.) Journal of immunology (Baltimore, Md. : 1950), (1995 Aug 15) 155 (4) 2232-9. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB **CTL** activity is a major component of the host immune response associated with control of **HIV** replication in the course of infection. Emerging populations of **HIV** overcome the protective effector mechanisms with variant sequences unrecognized by **CTL**. Therefore, a critical element for containment of virus spread might be the establishment of an immune response against highly conserved epitopes. In this study, we selected a panel of nonamer or decamer peptides, with demonstrated binding **affinity** for HLA-A 0201, to define novel highly conserved envelope-derived epitopes of **HIV**-1. **CTL** activities were characterized from PBMC of five HLA-A2+, **HIV**-1-infected individuals given recombinant gp160. **CTL** activity derived from patient PBMC stimulated in vitro with peptide was demonstrated against at least two novel minimal env-encoded conserved epitopes. One epitope, KLTPLCVTL (aa 120-128), is highly conserved among **HIV**-1 strains of the B subtype. Analysis of a **CTL** clone reactivity to a distinct epitope (aa 814-823) demonstrated fluctuations in the recognition of peptides corresponding to natural virus variants found in vivo.

L51 ANSWER 114 OF 135 MEDLINE on STN

94267165. PubMed ID: 7515908. **Cytotoxic T cell** repertoire selection. A single amino acid determines alternative class I restriction. Bergmann C C; Tong L; Cua R V; Sensintaffar J L; Stohlman S A. (Department of Neurology, University of Southern California School of Medicine, Los Angeles 90033.) Journal of immunology (Baltimore, Md. : 1950), (1994 Jun 15) 152 (12) 5603-12. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB **CTL** responses are governed by intracellular Ag processing, **affinity** of peptides for MHC class I molecules, and the T cell repertoire. In this report we demonstrate that a class I Dd-restricted 10-mer **CTL** epitope within the gp160 envelope glycoprotein of **HIV**-1 strain IIIB (residues 318-327) contains a 9-amino acid peptide (residues 319-327), which efficiently binds to both the Dd and Ld class I molecules in vitro. The potential for broadening the naturally limited **CTL** response to include presentation on the Ld class I molecules in vivo was examined using a minigene-based vaccine strategy to insure cytosolic expression of "preprocessed" forms of the gp160 epitope. Immunization with recombinant vaccinia viruses (vac) expressing either the gp160 10 mer or 9 mer, both including an initiation methionine (M318-327 and M319-327, respectively), induced predominantly Dd-restricted **CTL** specific for native gp160. By contrast, recombinant vac expressing eight gp160 amino acids (M320-327) generated predominantly Ld-restricted **CTL** which are specific for synthetic gp160 peptides but not native gp160. The ability to induce Ld-restricted **CTL** suggests that the absence of an Ld-restricted response to native gp160 cannot be attributed to a limited T cell repertoire, but to inefficient processing of gp160 for presentation on Ld. The switch in class I restriction, controlled by a single amino acid within one epitope, demonstrates that nonanchor residues have a profound effect on differential MHC restriction and **CTL** induction. Thus, minigene-based vaccines expressing minimal epitopes may be useful in inducing a more

heterogeneous CTL response than previously appreciated.

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L51  ANSWER 129 OF 135     MEDLINE on STN
92107932.     PubMed ID: 1722325.    An optimal viral peptide recognized by
     CD8+ T cells binds very tightly to the restricting class I major
     histocompatibility complex protein on intact cells but not to the purified
     class I protein. Tsomides T J; Walker B D; Eisen H N. (Department of
     Biology, Massachusetts Institute of Technology, Cambridge 02139. )
     Proceedings of the National Academy of Sciences of the United States of
     America, (1991 Dec 15) 88 (24) 11276-80.  Journal code: 7505876. ISSN:
     0027-8424. Pub. country: United States. Language: English.
AB   CD8+ cytotoxic T lymphocytes recognize cell surface complexes
     formed by class I major histocompatibility complex (MHC-I) glycoproteins
     and antigenic peptides.  We have identified a peptide nonamer (termed IV9)
     derived from the human immunodeficiency virus that is over a
     millionfold more active (at subpicomolar concentrations) than peptide
     analogues longer or shorter by one or two amino acid residues.  Although
     IV9 does not detectably bind to isolated MHC-I molecules as measured by
     equilibrium dialysis, we quantitated its specific binding in unaltered
     form to MHC-I on intact cells.  Less than 1% of cell surface MHC-I forms
     complexes with IV9, which suffices to trigger maximal cytotoxic
     T-lymphocyte activity.  By contrast, a peptide dodecamer that includes
     the IV9 sequence and is active at micromolar concentrations does not bind
     to MHC-I on intact cells, raising the possibility that this longer peptide
     undergoes processing.  Using stoichiometrically iodinated IV9 to obviate
     the ambiguities associated with trace labeling methods, we measured the
     dissociation kinetics of purified peptide/MHC-I complexes isolated by
     affinity chromatography and found these complexes to be exceedingly
     stable (t1/2 = 200-600 hr).


=> d his

     (FILE 'HOME' ENTERED AT 19:42:02 ON 01 APR 2004)

     FILE 'USPATFULL' ENTERED AT 19:42:32 ON 01 APR 2004
                E FRANCHINI GENOVEFFA/IN
L1            7 S E3
L2            0 S ZDENEK HEL/IN
                E ZDENEK HEL/IN
L3            0 S HEL ZDENEK/IN S HEL ZDENEK/IN
L4            0 S GENE SHEARER/IN
L5            1 S SHEARER GENE/IN
                E SHEARER GENE/IN
L6            7 S E4
                E NACSA JANOS/IN

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                E FRANCHINI G/AU
L7          196 S E3 OR E4
L8           67 S L7 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L9           16 S L8 AND (MHC OR MAJOR HISTOCOMPATIBILITY OR CTL OR CYTOTOXIC T
L10           0 S HEL Z/AU S HEL Z/AU
                E SHEARER G M/AU
L11         358 S E3 OR E6 OR E7
L12         118 S L11 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L13          20 S L12 AND (MAJOR HISTOCOMPATIBILITY OR CTL OR CYTOTOXIC)
                E NACSA J/AU
L14          22 S E3 OR E4

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                E FRANCHINI G/IN
L15          18 S E3
L16          10 S L15 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
                E SHEARER G M/IN
L17          10 S E3
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L18            15 S E3 OR E2
                  E NACSA J/IN
L19             3 S E3

     FILE 'USPATFULL' ENTERED AT 20:09:31 ON 01 APR 2004
L20         31746 S (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L21         10927 S L20 AND (CTL OR CYTOTOXIC)
L22          1761 S L21 AND (HIV/CLM OR HUMAN IMMUNODEFICIENCY VIRUS/CLM)
L23           233 S L22 AND (CTL/CLM OR CYTOTOXIC/CLM)
L24           186 S L23 AND (VACCIN? OR IMMUNOGEN?)
L25           182 S L24 AND (PROTECT? OR PREVENT?)
L26            96 S L25 AND (DNA/CLM OR NUCLEIC ACID/CLM)
L27            33 S L26 AND AY<2000
L28             1 S US6656471/PN
L29             1 S US6319666/PN

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L30        139974 S (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L31          5709 S L30 AND (CTL OR CYTOTOXIC T CELL? OR CYTOTOXIC T LYMPHOCYTE?
L32           176 S L31 AND (ESCAPE OR EVASION)
L33            78 S L32 AND (VACCIN? OR PREVENT? OR THERAP?)
L34            98 S L32 NOT L33
                  E KOENIG M/AU
L35           107 S E3
L36             1 S L35 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L37           122 S E4-E12
                  E E12
L38            46 S E1-E12
                  E E12
L39            36 S E1-E12
L40           184 S L37 OR L38 OR L39
L41             2 S L40 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L42          9232 S L30 AND PY=1995
L43           407 S L42 AND (CTL OR CYTOTOXIC T LYMPHOCYTE? OR CYTOTOXIC T CELL?
L44            95 S L43 AND (THERAPY OR IMMUNOTHERAPY OR ADOPTIVE)
L45            92 S L44 NOT L32
L46           310 S L31 AND (FAIL?)
L47           289 S L46 NOT L32
                  E KOENIG S/AU
L48           103 S E3
L49            33 S L48 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L50           151 S L31 AND (AVIDITY OR AFFINITY OR TITER)
L51           135 S L50 NOT (L32 OR L47)

=> log off
ALL L# QUERIES AND ANSWER SETS ARE DELETED AT LOGOFF
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STN INTERNATIONAL LOGOFF AT 22:32:54 ON 01 APR 2004
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